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METABOLIC EFFECTS OF ACTH UPON PRE-EXISTING DIABETES MELLITUS*

STEFAN S. FAJANS, M.D.†, LAURENCE H. LOUIS, ScD. AND JEROME W. CONN, M.D.

From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan

THE production of a diabetic state in normal people by administration of ACTH has been demonstrated (1). In patients with diabetes mellitus administration of ACTH has been shown to result in a marked rise of blood sugar (2), and administration of cortisone has produced intensification of glycosuria and increased requirements for insulin (3, 4). An increase in excretion of ketone bodies occurs in patients with combined Addison's disease and diabetes mellitus when cortisone is given (5).

A study of the metabolic effects of ACTH given over a prolonged period of time to a patient with diabetes mellitus has not been reported. Although important, such an experiment is not justifiable in a patient with uncomplicated diabetes mellitus because of the danger of permanent intensification of the diabetic state. Recently the opportunity arose to study a patient with diabetes mellitus of long standing, who received a twenty-two-day course of ACTH in the hope of arresting a progressive subacute myelogenous leukemia. The clinical findings were as follows:

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† Research Fellow in Medicine of the American College of Physicians, 1949–1950.

CASE REPORT

This 28-year-old, married female[1] was admitted to University Hospital on January 19, 1950, with the chief complaints of weakness and bleeding since September, 1949. The patient's diabetes, which had been diagnosed in 1940 at the age of 18 years, displayed the labile behavior of severe juvenile diabetes mellitus. Since September 1949, she had complained of ease of fatigue, weakness, exertional dyspnea, palpitation, menorrhagia, bleeding of gums, epistaxes, ease of bruising, blurring of vision, and fever. There was no history of weight loss. The patient had been hospitalized on three occasions between November 1949 and January 1950, at Evanston Hospital, Illinois. Initial laboratory findings in November showed a hemoglobin of 3 Gm., RBC 990,000, WBC 23,700, with many immature cells, and 10,000 platelets. Between November 1949 and January 14, 1950, the patient received aminopterin and a total of 12 transfusions, with moderate hematologic and clinical improvement. During this therapy there developed a progressive thrombocytopenia with troublesome uterine bleeding.

Upon admission to University Hospital the patient was observed to be a pale, well-developed, well-nourished, young woman who appeared chronically ill. The blood pressure was 130/70, and the pulse was 100. There were numerous petechiae over the legs and ecchymoses over the thighs and arms. Fundoscopic examination showed massive hemorrhages. Several petechiae were noted in the conjunctivae and buccal mucous membranes. The gums were hyperplastic, purple, and bled easily. There were a few shotty lymph nodes in the axillae and inguinal regions. The heart was normal in size and rhythm. A grade III blowing, systolic murmur was heard at the apex. The liver was three fingerbreadths below the right costal margin and extended into the left upper quadrant. The spleen was not palpable. The remainder of the examination was not remarkable.

Laboratory findings[2] on January 23, 1950: Hb. 6.9 Gm. or 44 per cent; RBC 2.2 million; WBC 26,000; hematocrit—RBC 20, WBC 1; MCV 91. The differential count showed: myeloblasts 20, promyelocytes 5, myelocytes 19, neutrophilic metamyelocytes 17, nonsegmented neutrophils 3, segmented neutrophils 16, monocytes 2, large lymphocytes 11, small lymphocytes 7, and eosinophils 0. Many myeloblasts were large and atypical; some had prominent nucleoli and monocytoid characteristics. Rare platelets were seen. Except for 4 plus glycosuria, the urine was normal. Stools showed 4 plus blood with the guaiac test. Serum NPN was 34 mg. per cent. Aspirated sternal marrow showed essentially complete loss of normal marrow activity, with replacement by highly proliferative leukemic cells.

Hospital course: The patient received ACTH between January 28 and February 18, 1950. Her hospital course was characterized by frequent epistaxes, oozing from the gums, increase in petechiae, tarry stools, profuse menstrual flow, increase in weakness, and development of necrotic areas in her mouth. During this period she was given 18 transfusions which kept her hemoglobin between 30 and 55 per cent. In addition to a rise in the white count from 25,000 to 81,000 during ACTH administration, the leukemic cells became progressively more bizarre with poorer differentiation, and the platelets disappeared entirely. The results of repeated marrow aspirations substantiated these findings. After two weeks of ACTH administration the patient's face became rounder and fuller, and her voice seemed husky. During the last week of her life she went downhill rapidly. Generalized lymphadenopathy developed, with nodes mainly of pea-size. Two

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[1] Because of our special interest, this patient was kindly referred to us by Dr. A. R. Colwell, of Evanston, Illinois, who had followed her diabetes since its onset.

[2] We wish to thank Dr. M. M. Meyers and Dr. F. H. Bethell for the performance of the hematologic studies.

days before death the temperature rose to 101°, and signs of fluid appeared at the bases, followed by moist rales throughout both lungs. She became dyspneic and lapsed into unconsciousness six hours before death[3] on February 23, 1950.

METHOD OF STUDY

The patient was fed a constant, weighed diet for twenty-eight consecutive days. The diet contained 96 grams of protein, 157 grams of carbohydrate, and 181 grams of fat (2,640 cals.) A total of 72–76 units of insulin was given daily except for the ninth ACTH day, when she received a total of 96 units of insulin. After a five-day baseline period, ACTH (Armour) was given for a total of twenty-two days. The daily dosage of ACTH (Armour Standard), given in four divided doses at six-hour intervals, was as follows: first day, 25 mg.; second day, 50 mg.; third to thirteenth day, 100 mg.; fourteenth to sixteenth day, 150 mg.; and seventeenth to twenty-second day, 200 mg. On the three days following cessation of ACTH administration total dietary intake was not constant, due to a failing appetite. Intake of carbohydrate, however, remained constant.

The chemical methods employed were the same as those described

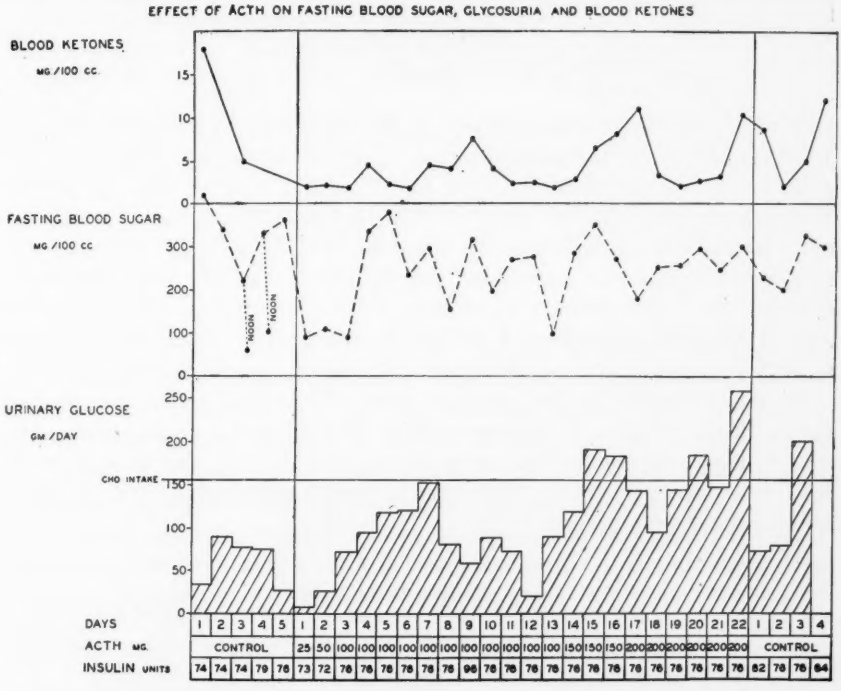

FIGURE 1

[3] The autopsy findings are summarized at end of article.

previously from this laboratory (1). In the quantitative determination of urinary uric acid, interference by glucose was eliminated by the use of the modification in method employed by Bien and Troll (6). Blood ketones were determined by the method of Weichselbaum and Somogyi (7), and total serum lipids by the method of Man and Gildea (8).

RESULTS

Fasting blood sugar and glycosuria: During the entire period of study the fasting blood sugar fluctuated between 200 and 400 mg. per cent (Fig. 1). During the baseline period glycosuria varied between 26 and 91

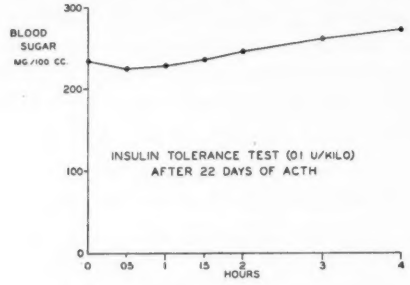

FIGURE 2

Gm. per twenty-four hours. When ACTH was given in a dose of 100 mg. per day, there was a gradual increase in glycosuria until it equalled the daily intake of carbohydrate (157 Gm.) on the seventh day of ACTH. With continuation of the same ACTH dosage (100 mg./day) the glycosuria decreased. Upon increasing the dose of ACTH to 150 mg. and 200 mg./day the glycosuria exceeded the dietary intake of carbohydrate on several days and reached a maximum of 258 Gm./day on the last day of ACTH. On discontinuation of ACTH the urinary loss of glucose decreased again for two days, with a rebound of glycosuria on the third day.

An insulin tolerance test was performed the morning after completion of the 22-day course of injections of ACTH. Figure 2 demonstrates the severe degree of insulin resistance which prevailed at this time. Insulin sensitivity was observed in the baseline period inasmuch as the following observations were made:

	Fasting blood sugar 8 A.M.	Blood sugar at noon
Baseline day #3	223 mg. %	56 mg. %
Baseline day #4	332 mg. %	108 mg. %

Nitrogen balance: The patient was in negative nitrogen balance during the control period (Fig. 3). In addition to glycosuria, the leukemia may have been a contributing factor. When ACTH (100 mg./day) was given, nitrogen excretion increased during the first five days and then decreased during the next six days. This was accompanied by the decreased glycosuria already noted. When the amount of ACTH was increased to 150 and 200 mg./day there was a significant increase in nitrogen excretion. This reached 38.3 Gm. per twenty-four hours on the last day of ACTH, when maximal glycosuria was observed.

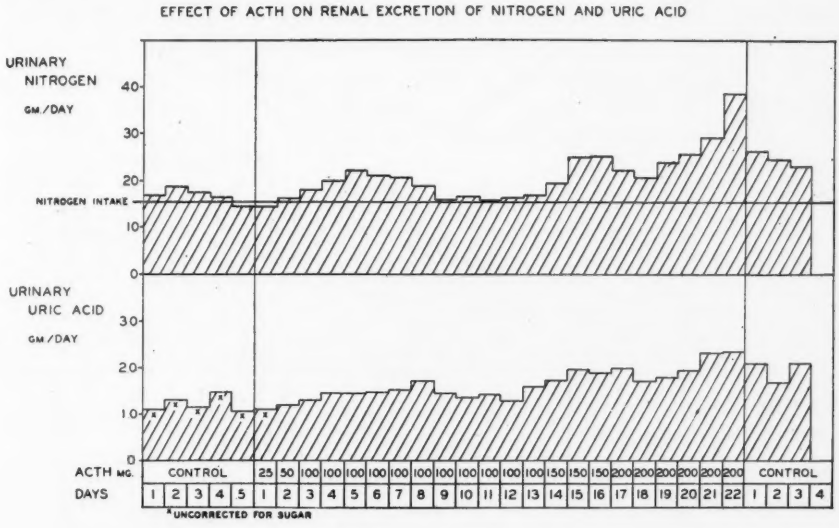
EFFECT OF ACTH ON RENAL EXCRETION OF NITROGEN AND URIC ACID
URINARY NITROGEN
GM./DAY
40
30
20
NITROGEN INTAKE
10
0
URINARY URIC ACID
GM./DAY
30
20
10
0
ACTH MG.
CONTROL
25 50 100 100 100 100 100 100 100 100 100 100 150 150 150 200 200 200 200 200 200
CONTROL
DAYS
1 2 3 4 5 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 1 2 3 4
* UNCORRECTED FOR SUGAR

FIGURE 3

Uric acid excretion: During the control period, uric acid excretion was considerably higher than usually seen. This can be related to the leukemia. As seen in Figure 3, urinary uric acid excretion increased further during ACTH administration, particularly with the larger doses. In general, the fluctuation of urinary uric acid paralleled the urinary nitrogen and glucose excretion and was maximal (2.38 Gm.) on the last day of ACTH.

Blood and urinary ketones: Ketone bodies in the urine were absent or minimal during the entire ACTH period. Figure 1 demonstrates that although mild ketonemia existed, baseline values were never exceeded during ACTH administration. This is surprising in view of the tremendous increase in renal excretion of glucose and nitrogen during the ACTH period.

Total lipids: Total serum lipids decreased during the period of administration of ACTH (Fig. 4).

11-Oxysteroids: During the baseline period the "cortin" excretion was in the high normal range (1.0–1.6 mg./24 hours). ACTH produced a considerable increase in 11-oxysteroid excretion (Fig. 4). There is a rough correlation between the excretion of 11-oxysteroids, nitrogen, and glycosuria during the period of administration of ACTH. This is interesting, in view of their fluctuations during the administration of constant amounts of ACTH.

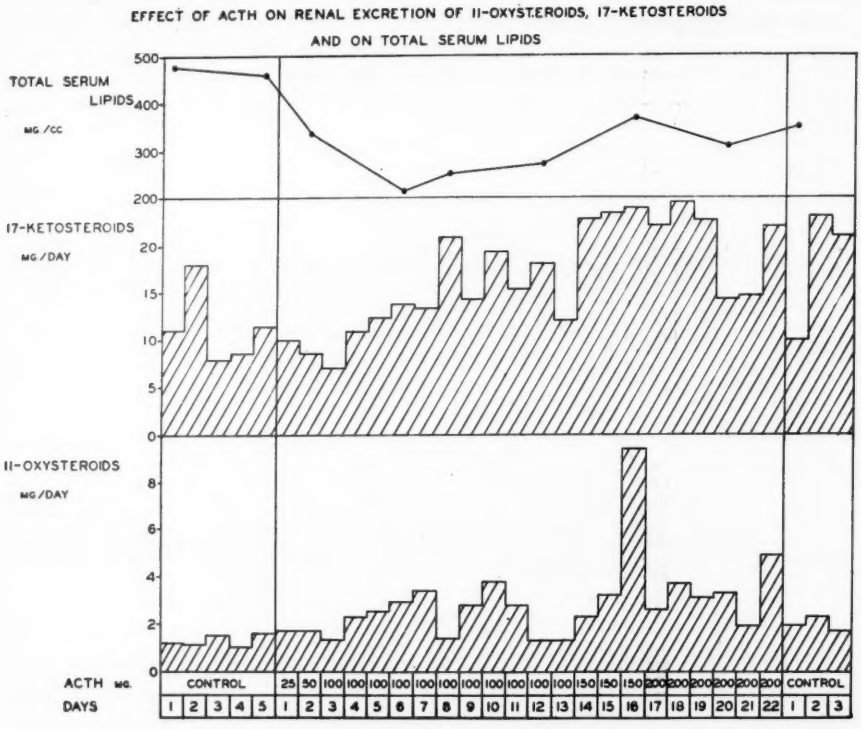

FIGURE 4

17-Ketosteroids: During the baseline period the excretion of 17-ketosteroids was normal for a young female. The increase in 17-ketosteroid excretion produced by ACTH was not great. Maximal rises again occurred with the larger amounts of ACTH (Fig. 4).

White blood cells: For two weeks before the administration of ACTH the total white cell count ranged between 19,000 and 26,000 per cu. mm. After the fourth day of ACTH there was a progressive rise of the total white cell count from 25,000 to 81,000 (Fig. 5) and the leukemic cells

showed progressive loss of differentiation. An eosinopenia (0–22 cells per cu. mm.) existed during the control period. During administration of ACTH the eosinophils ranged between 0 and 44 cells per cu. mm.

DISCUSSION

The increases in glycosuria and in urinary nitrogen during administration of ACTH were expected findings. The *degree* of suppression of utiliza-

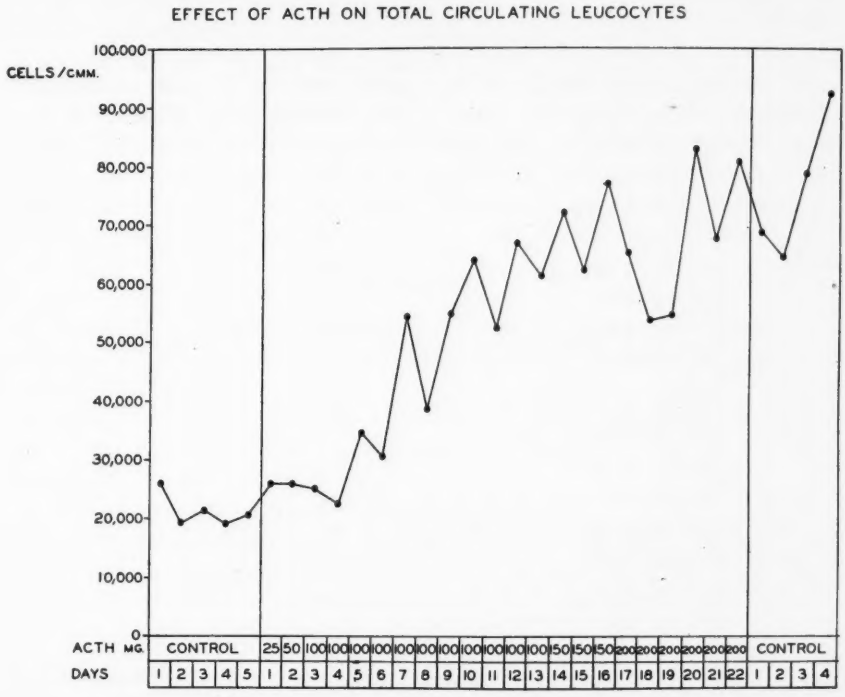

FIGURE 5

tion of carbohydrate merits comment. On several days the excretion of urinary glucose was in excess of the dietary intake of carbohydrate. This excess averaged 39 Gm. of glucose per day on the last three days of ACTH administration. Thus, in addition to the dietary carbohydrate, a considerable amount of the glucose derived from gluconeogenesis was lost in the urine, despite the administration of 76 units of insulin per day. This can be regarded as essentially complete resistance to insulin. The insulin tolerance test confirms this interpretation.

Under the metabolic conditions which existed, lack of greater accumula-

tion of ketone bodies in the blood and urine was indeed surprising. It would appear that some activity produced by administration of ACTH had "split off" the phenomenon of ketosis from the metabolic picture of total diabetes. Without additional data one can only speculate upon the possible mechanism which may have prevented development of severe ketosis. Two major possibilities exist: 1) increased capacity of the tissues to utilize ketone bodies, and 2) inhibition of ketogenesis.

TABLE 1. URINARY GLUCOSE EXCRETION AND DESTRUCTION OF BODY PROTEIN

Period, and no. of days	Average daily urinary glucose excretion (Gm./24 hrs.)	Average daily body protein breakdown (*Gm./24 hrs.)
Baseline—5 days	61	9
ACTH—3 days 25 mg., 50 mg., 100 mg.	35	5
ACTH—4 days 100 mg. daily	140	33
ACTH—3 days 100 mg. daily	75	12
ACTH—3 days 100 mg. daily	60	6
ACTH—3 days 150 mg. daily	163	48
ACTH—3 days 200 mg. daily	127	42
ACTH—3 days 200 mg. daily	196	100

* (Urinary nitrogen, Gm./24 hours×6.25)—96 Gm. from daily dietary protein intake. Destruction of body protein is actually somewhat greater, since fecal nitrogen has not been considered.

The tremendous breakdown of body protein could have been an important factor in inhibiting ketogenesis, if this protein were available to the body as a source of energy. Several factors militate against this interpretation; namely, significant amino aciduria which is known to occur during administration of ACTH, loss of some of the glucose of gluconeogenesis, and the potentiality of increased ketone formation from the remaining nonglycogenic amino acids. Unless ACTH has a direct inhibitory effect upon hepatic ketogenesis, present interpretations would favor increased ketolysis as the mechanisn

Table 1 shows some interesting relationships between glycosuria and breakdown of tissue protein during administration of ACTH. We are not prepared to make adequate interpretation of these data.

During the period of study there occurred a rise of the total white cell count with loss of differentiation of the cells of the granulocytic series and progression of the clinical manifestations of leukemia. Part of the acceleration of the leukemic process may have been due to disappearance of the effect of previous aminopterin therapy. In any case, ACTH did not impede the progression of the disease, and it is our impression that ACTH accelerated the downhill course. Dameshek *et al.* (9) observed progressive deterioration with ACTH therapy in 1 patient with subacute myelocytic leukemia previously treated with aminopterin, and failure of improvement in another patient with the same disease not previously treated with aminopterin. In 4 patients with acute granulocytic leukemia who had not received aminopterin, Pearson *et al.* (10) obtained transitory remissions upon administration of ACTH.

SUMMARY

1. A patient with juvenile diabetes mellitus and subacute myelogenous leukemia received a total of 2.875 Gm. of ACTH (Armour standard) in twenty-two days.

2. Glycosuria, which at times exceeded all available dietary carbohydrate, tremendous negative nitrogen balance, insulin resistance, and increased activity of the leukemia were observed.

3. Ketonemia and ketonuria were minimal or absent in the presence of essentially total diabetes and insulin resistance. Possible mechanisms which may be responsible for this unusual circumstance are discussed. ACTH appears either to accelerate the process of ketolysis in the body or to decrease hepatic ketogenesis.

Autopsy findings

Summary of pertinent gross pathologic findings: Hemorrhages in skin, mucous membranes, serosal surfaces, and myocardium. Hemopericardium, hemothorax, and hemoperitoneum. Moderate atherosclerosis of aorta and coronary vessels without gross calcification. Acute passive congestion and edema of lungs. Small discrete axillary and inguinal nodes. Hepatomegaly (2,540 Gm.) and splenomegaly (420 Gm.). Usual lobular structure of the pancreas, which weighed 60 Gm. The combined weight of the adrenal glands was 19.7 Gm. The adrenals were firm and were studded on the surfaces with multiple, 1-mm. nodules, which on section showed the same pale yellow color as the cortex proper.

Summary of microscopic findings: Lymphoblastomatous replacement of bone marrow and spleen: leukemic infiltrations in lymph nodes, heart, lungs, parathyroid glands, gastro-intestinal tract, omentum, liver, ovaries, and kidneys. Fatty atrophy of persistent hyperplastic thymus. Abundant colloid in thyroid acini. Pancreatic islets of Langerhans

were small and infrequent. With the Gomori technic, stainable beta or alpha cells could not be identified. There were no changes in the thymus or lymph nodes which could be attributed to ACTH. The adrenals showed moderate hypertrophy of cortical cells. In the zona glomerulosa there was an accumulation of intracellular lipids. The zona fasciculata showed marked loss of lipid material.[3]

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[3] Detailed histologic study of the adrenals is reported elsewhere (11).

URINARY PROLACTIN EXCRETION IN MAN*

RICHARD L. COPPEDGE, M.D.† AND
ALBERT SEGALOFF, M.D.

From the Departments of Physiology and Medicine, Tulane University of Louisiana and the Alton Ochsner Medical Foundation, New Orleans, Louisiana

PROLACTIN was the first pituitary hormone to be prepared in crystalline form (1), and various methods have been successfully used to extract it from pituitary tissue and to assay the material thus obtained. However, with one exception (2), no assay of prolactin excreted in human urine in terms of international units has been reported.

The purpose of this paper is to present a method of extraction and assay of prolactin excreted in human urine, together with some of the results of assays in patients.

Extraction procedure

1. Precipitation: To a 24-hour urine specimen, refrigerated during collection, are added 1 per cent by weight of sodium chloride and four volumes of 96 per cent ethyl alcohol. If the urine is not acid, it is acidified to litmus with acetic acid before addition of the alcohol. The precipitate is allowed to settle over night in the refrigerator, and collected by decantation and centrifugation. The precipitate is washed twice with 96 per cent alcohol, twice with ether, and dried.

2. Dialysis: After grinding, the precipitate is extracted with three 15-cc. volumes of distilled water, thirty minutes being allowed for each 15-cc. volume. The extract is dialyzed under refrigeration in a cellophane membrane against 6 hourly changes of 0.5 per cent sodium chloride.

3. Reprecipitation: The extract within the membrane is then treated as if it were an equivalent volume of urine, according to the method described in section 1. The final result is a dried precipitate.

PRELIMINARY STUDIES

Our first assay studies followed the local intradermal or micro method of Lyons (3) as modified by Hall (4). White Carneaux pigeons[1] (six to seven weeks old) were employed throughout. Four to 6 pigeons were used per specimen; a percentage of the unknown was injected over one crop sac and compared with a standard injected over the opposite sac. Usually

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† Post-doctorate Fellow of the National Institutes of Health.

[1] Obtained from the Palmetto Pigeon Plant, Sumter, S. C.

total doses of 0.25 per cent, 0.5 per cent and 1.0 per cent of the 24-hour urinary excretion were each compared with 0.25 I.U. and 0.5 I.U. of prolactin. Other dilutions of the unknown were also used occasionally. Injections were given daily for four days and autopsy was performed on the fifth day following a 16-hour fast.

This method proved to be unsatisfactory for several reasons. First, the assay involves a difficult subjective interpretation. Second, the best

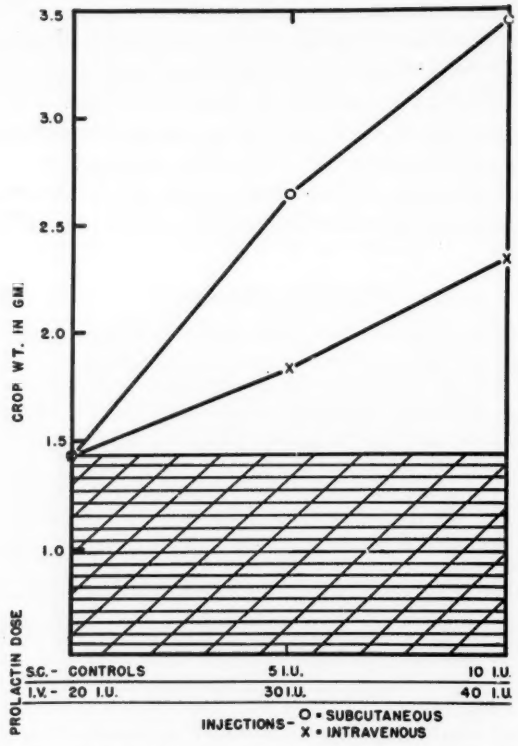

FIG. 1. Comparative effectiveness of intravenously and subcutaneously administered hypophyseal prolactin.

that could be done was to establish a wide range of values. Third, the nonspecific inflammatory reaction at the site of injection of the urinary extract frequently rendered interpretation of the assay difficult or impossible. We believe that this inflammatory reaction may also have prevented part of the prolactin from reaching the crop, thus producing an assay result lower than the true value.

Systemic assay according to the method of Riddle, Bates and Dykshorn

(5) was then attempted. In this method daily subcutaneous injections are given for four days; the weight of the crop sac excised on the fifth day is the end point. However, the entire crop is weighed, rather than only the two lateral crop sacs. This has the disadvantage of weighing a small part of the crop which is not stimulated but, on the other hand, avoids the error in estimating the area of the crop sac. The pigeons are killed by decapitation after an overnight fast. The crop is removed along with an excess of esophagus and stomach, is spread flat, and is then trimmed where the esophagus widens and above the line where the rugae of the stomach

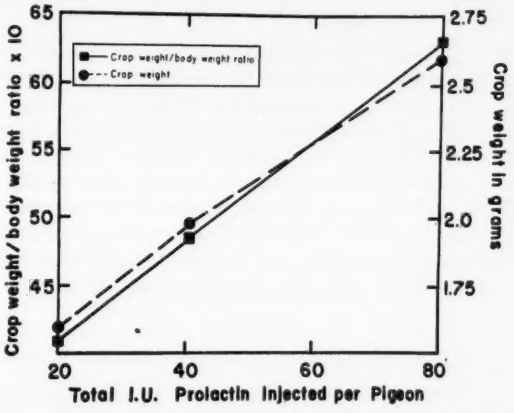

FIG. 2. Dosage response curves for intravenously injected prolactin.

begin. The crop is then opened, cleared of any milk or remaining food, blotted dry on a towel, and weighed at once.

The results of urinary extract assay by the systemic subcutaneous injection method were uniformly disappointing. The highest prolactin value by subcutaneous assay was 12.8 I.U. per twenty-four hours, in a specimen which assayed 100 I.U. per twenty-four hours by the local intradermal method and which had shown little inflammatory reaction on the latter assay. Furthermore, there was no correlation between values on the same specimen obtained by the two methods of assay. Those specimens which on local assay produced the greatest inflammatory reaction usually showed the lowest values on subcutaneous assay. This was the case even with those specimens which had shown high values by the local method.

The possibilities of intravenous assay were then investigated. Bates and Riddle (6) had previously reported the intravenous route to be approximately one-tenth as effective as subcutaneous injection. In Figure 1, average crop weights resulting from subcutaneous and from intravenous injections of prolactin standard are compared. These data agree with the

results reported by Bates and Riddle (6). Especially important is the fact that the average crop weight of uninjected birds is almost exactly that of pigeons receiving a total of 20 I.U. intravenously. When higher doses of prolactin were injected (Fig. 2) a straight line relationship between dose and response was found. The crop weight/body weight ratio as suggested by Bates (7) is used in an effort to allow partial correction for the considerable variation in body weight of individual pigeons.

Proposed assay procedure

The method used for assay of the precipitated residue obtained from the extraction procedure is as follows:

The residue is finely ground and extracted with 35 cc. of distilled water for two hours at room temperature. After centrifuging, the supernatant liquid is decanted and diluted to 40 cc. with addition of 100 I.U. of prolactin and distilled water. Two cubic centimeters of each specimen is injected intravenously into each of 4 pigeons daily for four days so that each bird receives a total of 20 I.U.+20 per cent of the unknown. The 40 cc. total available amount is adequate for injection and wastage, and usually dilute enough to prevent fatal toxic effects, yet not so dilute as to prevent the crop sac response. All solutions are kept in the refrigerator. Control groups are also given total doses of 20 I.U. and 80 I.U. intravenously. A curve is then prepared from the control values and the results of the assay calculated from the simultaneously obtained reference curve.

RESULTS

Recoveries of sheep hypophyseal prolactin added to urine were tested by the intravenous method. A pooled 96-hour urine specimen was divided

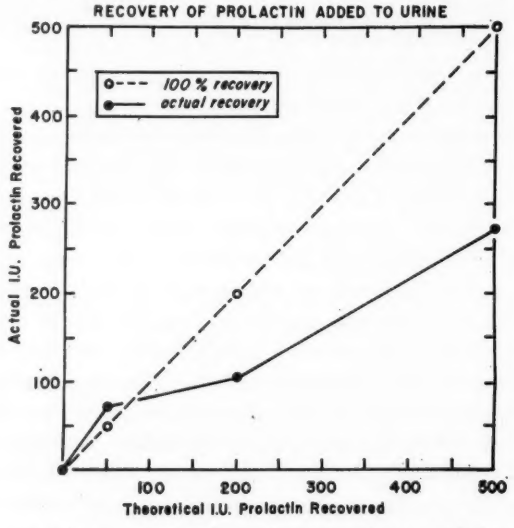

FIG. 3. The recovery of hypophyseal prolactin added to a pooled 96-hour urine specimen.

into four equal parts, to three of which were added 50 I.U., 200 I.U. and 500 I.U., respectively. Recovery of the added prolactin was computed by subtracting the prolactin from the assay values of the other specimens. Complete and actual recoveries are indicated in Figure 3.

Both local and intravenous assays were carried out on 43 specimens. A summary of the results is shown in Table 1. It may be noted that although there is approximate agreement between the two methods, the average value by intravenous assay falls above or in the upper part of the range by local assay; 28 per cent of the intravenous assays were higher than the corresponding local assays, and only 2 per cent were below.

TABLE 1. COMPARISON OF LOCAL AND INTRAVENOUS METHODS

Value per 24 hrs. by local assay	No. of specimens assayed	Average I.V. value per 24 hrs.	I.V. assays >10% above local value		I.V. assays >10% below local value		I.V. assays agreeing (±10%) with local value	
			No.	%	No.	%	No.	%
< 50 I.U.	16	42 I.U. (0–171)	3	19	0	0	13	81
> 50<100 I.U.	11	99 I.U. (63–148)	3	27	0	0	8	73
100 I.U.	7	140 I.U. (58–300)	4	57	1	13	2	30
> 50<200 I.U.	4	148 I.U. (63–251)	1	25	0	0	3	75
>100<200 I.U.	4	212 I.U. (142–305)	1	25	0	0	3	75
>200 I.U.	1	390	0	0	0	0	1	100
Total	43		12	28%	1	2%	30	70%

The urinary prolactin excretions of several normal male and female subjects have been assayed and are summarized in Table 2. Assays were repeated on 2 specimens from E. R. with similar results. Additional data are given on variations in prolactin excretion during the menstrual cycle in 2 normal parous females and in 1 with persistent lactation (Fig. 4). From the figure, it is apparent that in all 3 subjects there was a peak in excretion which followed the estimated time of ovulation.

TABLE 2. THE URINARY EXCRETION OF PROLACTIN BY NORMAL SUBJECTS

Normal females						Normal males				
Subject, age and color			Pre- or post-ovulatory	Excretion in I.U./24 hrs.		Subject, age and color			Excretion in I.U./24 hrs.	
				Local	Intravenous				Local	Intravenous
J.S.	23	W	post	<25	—	W.S.	6	W	—	0
E.R.	26	W	post	<50	—	N.S.	8	W	—	0
				20		J.M.	21	W	—	8
			pre	25	—	J.A.	21	W	—	103
				20		G.P.	23	W	—	62
			post	>25<50	—	J.S.	25	W	—	0
R.A.	30	W	pre	100	—	H.M.	25	W	—	137
			post	100	—	J.H.	26	W	<50	0
			pre	60	—	R.C.	27	W	> 50<100	—
			mid	<50	—				> 50<100	—
			post	>50<100	87				<50	116
C.G.	35	W	post	—	70				—	101
			post	>25<100	—	N.Z.	49	W	<25	10
H.S.	41	W	post	—	151	H.M.	50	W	> 50<100	148
R.J.	43	C	post	—	52	D.A.	75	W	>100<200	305
L.S.	65	W	menopa.	—	210					

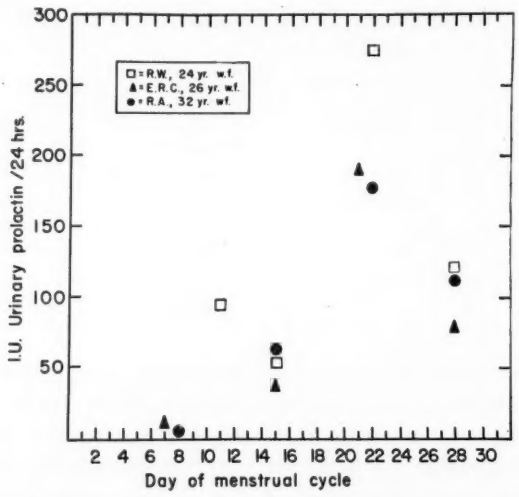

FIG. 4. Urinary prolactin assayed by the proposed intravenous method in E.R.C. and R.A., normal females, and in R.W., a patient with persistent lactation. All figures represent collections during a single menstrual cycle.

TABLE 3. THE URINARY EXCRETION OF PROLACTIN IN VARIOUS CLINICAL CONDITIONS

Pt.	Sex	Age	Color	Clinical data	Pre- or post-ovulatory	Urinary prolactin, I.U./24 hrs.	
						Local method	Intravenous method
A.G.	f.	50	C.	Castrate with lactorrhea of 1 year's duration			201
				After 15 mg. stilbestrol daily			108
J.P.R.	f.	40	W.	Castrate with pituitary tumor, & diabetes mellitus			116
						>50<100	83
				After 10 mg. stilbestrol daily			140
							48
I.W.W.	f.	25	W.	Lactorrhea with persistent amenorrhea, 3 years post partum			0
J.W.	f.	30	W.	Leiomyoma	Post		13
O.B.	f.	31	C.	Leiomyoma	Post	<50	
E.J.	f.	33	C.	Leiomyoma	Post	<25	
C.G.	f.	33	C.	Leiomyoma	Post	>50<200	87
M.M.	f.	35	C.	Leiomyoma	Post	<33	
V.B.	f.	37	C.	Leiomyoma	Post	<50	
C.J.	f.	39	C.	Leiomyoma	Post	<50	
M.D.	f.	2	C.	Constitutional precocious puberty. Menses since birth		>25<50	50
P.C.	f.	3	W.	Constitutional precocious puberty		>50<200	
G.A.C.	f.	13 mo.	W.	Precocious puberty, enlarged clitoris, labial hair			7
F.W.	m.	3½	W.	Precocious puberty			50
S.T.	f.	5	W.	Precocious puberty, pubic hair, breast growth, no menses			0
M.T.	f.	7	W.	Precocious puberty, adrenogenital syndrome			85
C.R.P.	f.	69	W.	Acromegaly		50	
L.S.	f.	45	W.	Acromegaly		40	
J.M.	f.	40	W.	Sheehan's syndrome		<20	
C.G.	m.	20	C.	Panhypopituitarism. (After 2000 I.U. chorionic gonadotropin daily)			87
M.P.	f.	21	W.	Secondary amenorrhea			133
W.D.	f.	23	W.	Secondary amenorrhea			10
J.J.	f.	27	C.	Sterility, unexplained	Pre		13
					Post		0
O.D.	f.	23	W.	Sterility, unexplained			5
R.A.	f.	36	C.	Sterility, unexplained. (G.S.H. >192 M.U./24 hrs.)			27
I.P.	m.	27	W.	Bilateral testicular atrophy		<25	
C.H.	f.	23	W.	Hirsutism		<50<100	0
H.S.	f.	35	W.	Chronic cystic mastitis	Post	250	
					Pre	125	
J.F.	f.	41	W.	Chronic cystic mastitis			0
C.B.	f.	37	W.	Cushing's syndrome, adrenal carcinoma. (17-KS, 101–924 mg./24 hrs.)		>100<200	

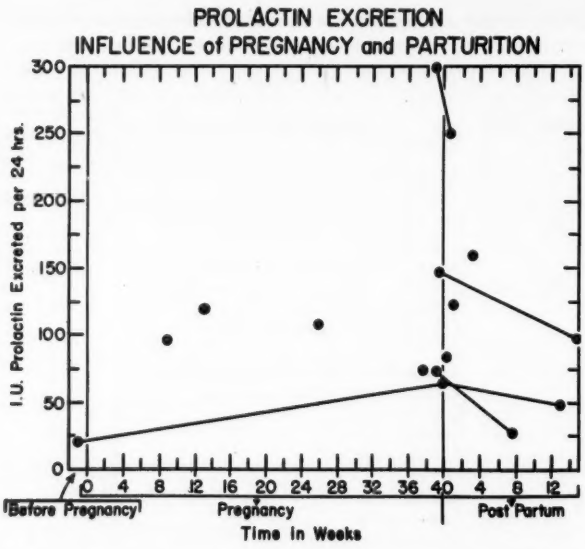

FIG. 5. Influence of pregnancy and parturition on prolactin excretion. In each instance the values connected by a line are from the same patient.

The prolactin excretion values of individuals with various clinical conditions are given in Table 3. Assay values on patients during pregnancy and lactation are listed in Figure 5. Additional values for parturition and after stilbestrol therapy during lactation are shown in Tables 4 and 5, respectively.

DISCUSSION

The experiment in which prolactin was added demonstrated that approximately half of the added hypophyseal prolactin was lost during the extraction procedure. One attempt to purify our extract further by acid-acetone extraction resulted in total loss of the assayable activity.

TABLE 4. INFLUENCE OF PARTURITION ON URINARY PROLACTIN EXCRETION

Pt.	Age	Ante partum			Post partum		
		Days A.P.	Prolactin, I.U./24 hrs.		Days P.P.	Prolactin, I.U./24 hrs.	
			I.V. method	Local method		I.V. method	Local method
B.F.	24	8	300	>100<200	3	251	>50<200
M.M.	24	6	73	> 50<100	3		>50<100
S.Y.	35	2		100	7	123	>50<100

There are two possible reasons for the discrepancy between the magnitude of our results and those of Meites and Turner (2). One may be their use of an acid-acetone extraction procedure, which although successful with pituitary tissue, led to loss in our hands when applied to an already partially purified urinary extract. The other may be the possible lack of absorption of prolactin at the site of the intradermal injection employed in their studies.

In the few cycles studied in normal women, the time of the cycle had a notable effect on the prolactin excretion. There appears to be a peak beyond mid-cycle, and the later values are higher than the earlier ones. It is interesting to speculate upon whether this indicates a role for prolactin

TABLE 5. INFLUENCE OF STILBESTROL ON PROLACTIN EXCRETION, IN SUPPRESSING LACTATION

Pt.	Age	Days post partum	Before therapy		After therapy	
			Prolactin, I.U./24 hrs.		Prolactin, I.U./24 hrs.	
			I.V. method	Local method	I.V. method	Local method
G.S.	26	1	83		108	
E.C.	24	21	106	100	110	100

in progesterone secretion, and whether the higher postovulatory values might possibly indicate that prolactin is luteotropic in man as well as in the rodent. To carry this speculation still further, although Segaloff and coworkers (8) were unable to show regression of leiomyomas during progesterone therapy, this steroid may play a part in the genesis of these tumors. Thus the distinctly low prolactin excretion in patients with leiomyomas may be related to the genesis of the uterine tumors. These observations appear to us to constitute the first objective indication that prolactin is luteotropic in man.

Among the abnormal subjects, fairly consistent results within each group were obtained in those with precocious puberty and in those with sterility. The prolactin values of children with precocious puberty reflect an elevation, when compared with the values obtained in 2 normal children of similar ages. In M. T., aged 7 years, the elevated excretion may be an indication of pituitary stimulation by adrenal steroids, as is also possibly the situation in the case (C. B.) of Cushing's syndrome with adrenal carcinoma.

Treatment with testosterone propionate in many patients with carcinoma of the breast has been found to lead to increases in prolactin excre-

tion (9). It is interesting that chorionic gonadotropin, as in the case of C. G. (panhypopituitarism), has also been shown to increase prolactin excretion (10), and one may speculate that at least one of its pathways of action may be via pituitary stimulation. The few cases of unexplained sterility all had low values.

Pregnancy and lactation. The results presented here indicate that there may be a gradual rise in prolactin excretion during pregnancy, no sudden change at parturition, and a gradual decline following delivery despite the maintenance of lactation. The number of assays, especially those repeated on a single subject, are inadequate, and the results are therefore equivocal. The trends indicated here are partly at variance and partly in agreement with previous theories of induction and maintenance of lactation, a few of which may be briefly mentioned here.

Nelson (11) ascribed suppression of lactation during the later months of pregnancy to estrogenic inhibition of hypophyseal prolactin effectiveness. He noted that estrone was capable of inhibiting prolactin induction of lactation in properly prepared guinea pigs, and that this was not affected by the presence or absence of the pituitary. Meites and Turner (12) observed, however, that increasing doses of diethylstilbestrol produced successive increases in the prolactin content of adult guinea pig pituitaries, although in immature guinea pigs, an optimum intermediate dose was found to produce maximum pituitary stimulation, with higher doses producing a fall in prolactin content. These workers found that concomitant administration of relatively large doses of progesterone abolished the stimulatory effect of estrogen; they then suggested that lactation was induced because progesterone levels were thought to fall more rapidly than estrogen levels after delivery, thus allowing unimpeded estrogenic stimulation of the pituitary. Foley and Malpress (13) used the observation of Meites and Turner of an optimum intermediate estrogen titer in immature guinea pigs, together with other evidence, to form the basis of a thesis that the high estrogen levels of pregnancy inhibit the pituitary, but that in falling at parturition, they pass through a stimulatory range. More recently Walker and Matthews (14) have offered evidence to show that the combined action of estrogen and progesterone in stimulating mammary proliferation is effective. These authors, like Nelson, attribute the inhibition of lactation, at least in part, to the local action of these steroids on the mammary gland.

The results presented here show no great change in prolactin excretion of humans soon after delivery. This suggests that induction of lactation comes about as a result of the removal of local (or mammary) factors in inhibition of lactation which occurs as the progesterone and estrogen levels fall. Prior to parturition, pituitary prolactin secretion has apparently been stimulated continuously by the high blood steroid levels. Although there

may not be a continuous increase in prolactin production, its secretion appears to be at least sustained until delivery, in contrast to the variations during the menstrual cycle. After delivery, the excretion was shown to fall somewhat in 3 subjects, despite continued nursing. This fall may be presumably due to removal of stimulating estrogens. That the fall is not more precipitate, may be ascribed to the suckling stimulus, as suggested by Selye and McKeown (15) and others. In this respect, it is interesting that in the woman whose prolactin excretion was 49 I.U. per twenty-four hours, after fourteen weeks' nursing, the excretion fell to 0 I.U. in twenty-four hours one week after discontinuing nursing; it is probably significant that she did not take estrogen concomitantly. In contrast to this complete fall are the values obtained in 2 subjects (Table 5) who were given diethylstilbestrol at the time nursing was discontinued.

A drop in prolactin excretion occurred in 1 patient during pregnancy. It may be of interest, particularly in view of the possible identity of prolactin and luteotropin, that a preeclamptic toxemia of pregnancy developed in this patient at about the time the second specimen was received for assay.

SUMMARY

A method is presented for extraction and assay of prolactin excreted in human urine, which appears to give consistent and reproducible results.

Normal males had urinary excretions of prolactin ranging from 0 to 306 I.U. The prepubertal boys had no assayable prolactin, whereas the oldest man (75 years) excreted the greatest amount.

There is a distinct variation during the menstrual cycle in normal women with peak values attained after mid-cycle.

The assay values in a few endocrinopathies and during pregnancy and lactation are also presented.

Acknowledgment

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SEXUAL TRENDS IN FEMALE PSEUDOHERMAPHRODISM

FRANK HINMAN, JR., M.D.

From the Department of Surgery-Urology, University of California School of Medicine, San Francisco, California

OUR recent decision to reverse the sex of 2 female pseudohermaphrodites with adrenal cortical hyperplasia by plastic repair of the phallus (1) made imperative a detailed study of previous experience of others with the course of the disease. We made 2 children into boys because we felt that the masculinization was progressive, as indicated by increased bone age, advanced secondary sex characteristics and elevated 17-ketosteroid excretion, and that it seemed advisable for the children to be reared in the sex into which each would best fit physically, socially, and therefore psychologically.

MATERIAL

Records of 149 patients reported in the literature since 1816 have been reviewed and tabulated. Five cases which we have ourselves observed are included in the tables.

This material was arbitrarily divided into two groups. Data on all patients reported upon after the age of 15 are assembled in Table 1; those cases reported before the patient reached the age of 15 are listed in Table 2. The reason for the separation is that only after puberty are physical and psychologic traits completely evolved, allowing estimation of environmental and hormonal forces. It must be obvious that data assembled from such diverse sources are incomplete and can be subjected to varying interpretation. Every attempt has been made, however, to record the clinical notations objectively. The recording of adrenal hyperplasia and familial incidence, plus the fact that most female pseudohermaphrodites who have been thoroughly studied have adrenal cortical hyperfunction, makes inaccuracies less frequent.

DISCUSSION

From the point of view of treatment of the female pseudohermaphrodite, we are interested principally in those reported cases in which the patients were old enough to show the full effect of the hormonal masculinization. For that reason, Table 1 is of greater interest than Table 2, because

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TABLE 1. FEMALE PSEUDOHERMAPHRODITES OVER THE AGE OF 15 YEARS

No.	Author and reference	Age when seen (yrs.)	Environmental sex	Hyperplasia of adrenals	Familial	Age at clitoridectomy (yrs.)	Final sex	Comment
1	Merry & Cooper: *Guy's Hosp. Rep.* **5**: 243, 1840	86	Female	?	?	0	Female	Disliked men.
2	de Crecchio: *Wien. med. Presse* **30**: 763, 1866. (Quoted in *Tr. Path. Soc. London*, **56**: 189, 1905)	45	Male	Yes	?	0	Male	Refused marriage by church, since baptized as a female.
3	Ogston: *Österr. Jahrb. f. Paed.* **2**: 180, 1872. (Quoted in *J. Obst. & Gynaec. Brit. Emp.* **28**: 23, 1921)	16	Female	Yes	No	0	Female	
4	Palmer: *Am. J. Obst. & Gynec.* **13**: 174, 1880	20	Female	?	Yes	0	Female	Had some masculine interests.
5	Palmer: *Ibid.*	22	Female	?	Yes	0	Female	Masculine interests.
6	Pozzi: *Gaz. méd. Paris* **2**(87): 109, 1885	17	Female	?	Yes	0	Male	Decided to be male at 17.
7	Pozzi: *Ibid.*	18	Female	?	Yes	0	Male	Decided to be male at 18.
8	Marchand: *Internat. Beitr. z. wissensch. Med.*, Festschr. g.z. 70 Geburtstag v. R. Virchow, Verlag A. Hirschwald, Berlin **1**: 535, 1891	50	Female	Yes	No	0	Male	Sex changed medico-legally at puberty; first association of adrenal hyperplasia with female pseudohermaphrodism.
9	Blom: Reviewed in *Zentralb. f. Gynäk.* **19**: 685, 1895	49	Female	?	No	0	Female	Died after laparotomy, aged 49.
10	Engelhardt: *Monatschr. f. Geburtsh.* **12**: 729, 1900	59	Male	Yes	No	0	Male	Married older female, but not interested in females.
11	Fibiger: *Virchows Arch. f. path. Anat.* **181**: 1, 1905	58	Male	Yes	No	0	Male	Died of tuberculosis.
12	Fibiger: *Ibid.*	47	Male	Yes	No	0	Male	Married to female; had 3 children. (Wife said children not his own.)
13	Bouillaud & Manec (1833), *in* v. Neugebauer: Hermaphroditismus beim Menschen, Klinkhardt, Leipzig, 1908	62	Male	?	No	0	Male	Married to female.
14	Johnston: *Surg., Gynec. & Obst.* **7**: 227, 1908	23	Male	?	?	0	Male	Married to female.
15	Küstner: *Ztschr. f. Geburtsh. u. Gynäk.* **73**: 816, 1913	37	Female	?	Yes	0	Female	Liked females better than males.
16	Fraenckel: Virchows *Arch. f. path. Anat.* **215**: 378, 1914	41	Female	Yes	Yes	0	Female	
17	Maicher: Inaug. Diss., Breslau, 1923	32	Female	?	Yes	0	Female	Sister of Fraenckel's and of Küstner's patients.
18	Löser & Israël: *Ztschr. f. urol. Chir.* **13**: 75, 1923	21	Female	Yes	Yes	21	Female	No follow-up.
19	Löser & Israël: *Ibid.*	19	Female	?	Yes	?	? Female	No follow-up.
20	Gal: *Zentralbl. f. Gynäk.* **48**: 1203, 1924	20	Female	?	Yes	20	Female	No follow-up.
21	Gal: *Ibid.*	21	Female	?	Yes	21	Female	No follow-up.
22	Wereschinski: *Arch. f. klin. Chir.* **129**: 810, 1924	29	Female	Yes	Yes	0	Female	? Tumor in congenital case. Sister had same disorder.
23	Blair Bell: *Am. J. Obst. & Gynec.* **10**: 778, 1925	31	Female	No	Yes	31	Female	Sister had same abnormality; both acted as females.
24	Fruchaud & Vialle: *J. d'urol.* **21**: 525, 1926	17	Male	?	Yes	0	Male	Explored for twisted ovarian cyst. Brother of Case 25; quite masculine.
25	Fruchaud & Vialle: *Ibid.*	24	Male	?	Yes	0	Male	Brother of Case 24. Explored for twisted ovarian cyst also.
26	Priesel: *Handb. spez. path. Anat. u. Histol.* **6**: (Pt. 3) 1, 1931	79	Female	Yes	No	0	Female	
27	Auvray & de Pfeffel: *Bull. d'Obst. & Gyn. Soc.* p. 321, 1912. (Cit. in *Endokrinologie* **14**: 225, 1934)	72	Female	Yes	No	0	? Female	Male external genitalia.

TABLE 1—*Continued*

No.	Author and reference	Age when seen (yrs.)	Environmental sex	Hyperplasia of adrenals	Familial	Age at clitoridectomy (yrs.)	Final sex	Comment
28	Finkler: *J.A.M.A.* **102**: 924, 1934	16	Female	No	No	16	Female	Estrogens gave good result at first only.
29	Monsch: *Schweiz. med. Wchnschr.* (N.S.) **15**: 509, 1934	56	Male	No	No	0	Male	? Adrenogenital syndrome.
30	O'Farrell: *J.A.M.A.* **104**: 1968, 1935	19	Female	?	No	19	Female	Much improved by hormonal therapy.
31	O'Farrell: *Ibid.*	24	Female	?	No	24	Female	Menses followed simple clitoridectomy.
32	Young: Genital Abnormalities, etc., 1937 (2)	16	Female	Yes	Yes	16	Female	Had partial adrenalectomy.
33	Young with Quinby (1916): *Ibid.*	31	Male	?	No	0	Male	Committed suicide, aged 31, when priest forbade marriage.
34	Young: *Ibid.*	16	Female	?	Yes	0	Male	Pleased at being boy. Brief report.
35	Broster *et al.*: The Adrenal Cortex and Intersexuality. Chapman & Hall, London, 1938	16	Female	Yes	No	0	Female	Felt feminine after left adrenalectomy; weakly homosexual.
36	Broster *et al.*: *Ibid.*	26	Female	Yes	No	6	?	Wanted to be a boy. Died of postoperative shock after left adrenalectomy.
37	Dorfman *et al.*: *Endocrinology* **27**: 1, 1940	15	Female	Yes	No	0	Female	Left adrenalectomy and estrogens probably made patient worse.
38	Haynes *et al.*: *Med. Rec.* **154**: 307, 1941	43	Male	No	No	0	Male	Oophorectomy, etc., aged 25 (? adrenogenital syndrome).
39	Chanis, Jr.: *J. Urol.* **47**: 508, 1942	18	Male	No	No	0	Male	Breasts removed; was married to female (? adrenogenital syndrome).
40	Genitis & Bronstein: *J.A.M.A.* **119**: 704, 1942	15	Female	Yes	No	?	?	Partial adrenalectomy; no details.
41	Kozoll: *Arch. Surg.* **45**: 578, 1942	23	Female	?	No	23	Female	Seclusive.
42	Solomons: *J. Obst. & Gynaec. Brit. Emp.* **50**: 363, 1943	18	Female	Yes	No	0	Female	Good athlete. Advised against marriage.
43	Bayer: *Psychosom. Med.* **9**: 246, 1947	19	Female	Yes	No	19	Female	Partial adrenalectomy without feminization.
44	Cotte: *J. Mt. Sinai Hosp.* **14**: 170, 1947	16	Male	?	No	16	Female	Pregnant twice; not at all masculinized (? adrenogenital syndrome).
45	Hain (Herzfield): *J. Path. & Bact.* **59**: 267, 1947	16	Male	?	No	9	Female	Estrin-formed breasts.
46	Hain (Gemmell): *Ibid.*	21	Female	Yes	Yes	0	Female	Estrogens had no effect?
47	Hain: *Ibid.*	16	Female	?	Yes	0	Female	Not much hirsutism; sister of Case 46.
48	Wilhelm: *J. Mt. Sinai Hosp.* **14**: 679, 1947	23	Female	Yes	No	23	Female	Partial adrenal resection and estrogens caused improvement.
49	Kulcsar: *Canad. M.A.J.* **59**: 144, 1948	16	Female	?	?	0	?	Chinese girl who wanted to be a boy; inadequate details.
50	Zahn: *Schweiz. med. Wchnschr.* **78**: 480, 1948	76	Female	Yes	?	0	Female	
51	Deming *et al.*: *J. Urol.* **61**: 144, 1949	23	Female	No	Yes	23	Female	Estrogens had no effect.
52	Deming *et al.*: *Ibid.*	42	Female	No	Yes	42	Female	Estrogens, etc., caused perhaps slightly more feminization.
53	Wilhelm: *Urol. & Cutan. Rev.* **54**: 34, 1950	Adult	Female	Yes	?	0	Female	Adrenalectomy caused improvement of breasts and body.
54	Hinman, Jr.: (In Press, 1950)	18	Female	Yes	No	5	Female	Partial adrenalectomy and estrogens improved breasts, but hirsutism pronounced.

TABLE 2. FEMALE PSEUDOHERMAPHRODITES LESS THAN 15 YEARS OF AGE

No.	Author and reference	Age when seen	Environmental sex	Age at clitoridectomy (yrs.)	Age at death, and cause	Comment
1	Otte: 1816. (Quoted by Young, 1937 (2))	Infant				Reference not available.
2	Curling: *Med. Times & Gaz.* 1852. (Quoted in *Arch. Ped.* **60:** 529, 1943)	Infant	? Female	0	Infancy; cause ?	Familial, with Case 3.
3	Curling: *Ibid.*	Infant	? Female	0	Infancy; cause ?	See Case 2.
4	Heppner: *Arch. f. Anat., Phys. u. wiss. Med.* 679, 1870	2 mo.	Female	0		Accessory adrenal tissue.
5	Ogston: *Osterr. Jahrb. f. Paed.* **2:** 180, 1872	5 yr.	Female	0	5 years; from diarrhea	Familial, with Case 6.
6	Ogston: *Ibid.*	12 yr.	Female	0	12 years; from diarrhea	See Case 5.
7	Pozzi: Gaz. méd. Paris **2**(87): 109, 1885	19 mo.	Female	0		Familial, with Cases 6 and 7, Chart I; probably raised as male.
8	Phillips: *Tr. Obst. Soc. London* **28:** 158, 1886	19 da.	Male	0	19 days; "wasted away"	Familial, with Cases 9, 10, and 11.
9	Phillips: *Ibid.*	29 da.	Female	0	24 days, wasted away, as in Case 8	See Case 8.
10	Phillips: *Ibid.*	59 da.	Female	0	59 days, from wasting	See Case 8.
11	Phillips: *Ibid.*	40 da.	Male	0	40 days, from wasting	See Case 8.
12	Krokiewicz: *Virchows Arch. f. path. Anat.* **146:** 525, 1896	5 da.	Female	0	5 days, from pneumonia	
13	Fibiger: *Ibid.* **181:** 1, 1905	6 wk.	Male	0	6 weeks, from "gastroenteritis"	
14	v. Neugebauer: Hermaphroditismus beim Menschen. Klinkhardt, Leipzig, 1908	Newborn	Female	0	At birth	Very large adrenals.
15	Koch: *Virchows Arch. f. path. Anat.* **196:** 207, 1909	Infant	Female	0	At birth, from asphyxia	Large adrenals.
16	Meixner; *Deutsche Ztschr. f. Chir.* **102:** 158, 1909	8½ mo.	Male	0	8½ months, from pneumonia	Adrenal rests.
17	Durlacher: *Deutsche med. Wchnschr.* **38:** 2127, 1912	20 mo.	Female	0	In infancy	Familial, with Case 18.
18	Durlacher: *Ibid.*	6 mo.	Female	0	In infancy	See Case 17.
19	Raubitschek: *Frankfurt. Ztschr. f. Path.* **10:** 206, 1912	1½ yr.	Female	0	1½ years, from "renal tumor"	Adrenal described as normal.
20	Martius: *Ibid.* **12:** 47, 1913	Infant	Female	0	In infancy	Multiple malformations; ? adrenogenital syndrome.
21	Benda: *Berl. klin. Wchnschr.* **51:** 66, 1914	2 mo.	Male	0		To be raised as male; large adrenals.
22	Reuben & Manning: *Arch. Pediat.* **39:** 769; **40:** 27, 1923	3 yr.	Female	0	3 years; cause ?	No details given.
23	Scabell: *Deutsche Ztschr. f. Chir.* **185:** 1, 1924	4 mo.	Male	0	4 months, from diarrhea	Brother had similarly enlarged adrenals and died in infancy.
24	Blair Bell: *Am. J. Obst. & Gynec.* **10:** 778, 1925	5 yr.	Female	5		To be raised as female.
25	Blair Bell: *Ibid.*	7 yr.	Female	7		To be raised as female.
26	Blair Bell: *Ibid.*	1 mo.	Female	Later		To be raised as female.
27	Feldman: *Virchows Arch. f. path. Anat.* **259:** 608, 1926	7 yr.	Male	0	7 years; from pneumonia	Adrenals hyperplastic (case of Stahr, 1923).
28	Manning *et al.*: *Am. J. Dis. Child.* **35:** 862, 1928	11 yr.	Female	11		Incomplete report.
29	Carnett: *Surg. Clin. North Amer.* **10:** 1325, 1930	5 yr.	Female	5		No follow-up.
30	Pryor & Brooks: *Arch. Pediat.* **47:** 779, 1930	7½ yr.	Female	7½		No details of adrenals.
31	Rupilius: *Arch. f. Kinderheilk.* **100:** 206, 1933	1 mo.	Female	0	Infancy, from pneumonia	Familial, with Case 32.
32	Rupilius: *Ibid.*	4 mo.	Female	0	Infancy; cause not given	Familial, with Case 31. Both patients had large adrenals.
33	Priesel: *in* Henke & Lubarsch Handbuch, **6:** (Pt. 3) 1, 1932	5½ yr.	Male	0	5½ years, from scarlet fever	Large adrenals and precocious development.
34	Bayer & Lang: *Endokrinologie* **14:** 225, 1934	Infant	?	0	Newborn; cause not given	Large adrenals.
35	Bayer & Lang: *Ibid.*	1 mo.	Female	0	1 month; cause not given	Hyperplastic adrenals.
36	O'Farrell: *J.A.M.A.* **104:** 1968, 1935	9 yr.	Female	9		Sister died, aged 3, as a pseudohermaphrodite; 3 cousins pseudohermaphroditic.
37	Werthemann: *Schweiz. med. Wchenchr.* **16:** 218, 1935	12 wk.	? Female	0	12 weeks; cause not given	Familial, with Cases 38 and 39; also 2 brothers with large adrenals and hypospadias.

TABLE 2.—*Continued*

No.	Author and reference	Age when seen	Environmental sex	Age at clitoridectomy (yrs.)	Age at death, and cause	Comment
38	Werthemann: *Ibid.*	4 wk.	? Female	0	4 weeks; cause not given	See Case 37; all had large adrenals.
39	Werthemann: *Ibid.*	2½ wk.	? Female	0	2½ weeks	See Case 37.
40	Neumann: *Arch. f. Gynäk.* **160:** 481, 1936	6½ wk.	Female	0	?	No details; adrenals hyperplastic.
41	Jacobziner & Gorfinkel: *Am. J. Dis. Child.* **52:** 308, 1936	4⅛ yr.	Female	Later		Advocated unilateral adrenalectomy at puberty.
42	Jacobziner & Gorfinkel: *Ibid.*	4½ yr.	Female	Later		See Case 41.
43	Weyeneth: *Virchows Arch. f. path. Anat.* **297:** 594, 1936	4 mo.	Male	0	4 months; ? adrenal insufficiency	Adrenals hyperplastic.
44	Zaudy: *Endokrinologie* **17:** 372, 1936	13½ yr.	Female	Later		To wait until puberty before operation or hormonal treatment.
45	Polzer & Priesel: *Frankfurt. Ztschr. f. Path.* **51:** 257, 1937	5 mo.	? Female	0	5 months, from infection	Hypertrophied adrenals.
46	Polzer & Priesel: *Ibid.*	2 mo.	Female	0	2 months, from infection	Hypertrophied adrenals.
47	Young: Genital Abnormalities, etc., 1937 (2)	6 yr.	Female	6		Partial adrenalectomy.
	Wilkins *et al.*: *Bull. Johns Hopkins Hosp.* **86:** 249, 1950	15 yr.	Female			Treated with cortisone, with 17-ketosteroid suppression.
48	Young: Genital Abnormalities, etc., 1937 (2)	12 yr.	Female	12		Sister of Case 32, Chart I; partial adrenalectomy without effect.
49	Young: *Ibid.*	4 yr.	Female	4		
50	Young: *Ibid.*	6 yr.	Female	0		No details; familial, with Case 34, Chart I.
51	Albert: *Zentralbl. f. allg. Path. u. Anat.* **71:** 291, 1938	Infant	Male	0	1½ months; cause not given	Hyperplastic adrenals.
52	Broster *et al.*: The Adrenal Cortex and Intersexuality, Chapman & Hall, London, 1938	13 yr.	Female	0		Right hyperplastic adrenal removed.
53	Velten & Noethe: *Frankfurt. Ztschr. f. Path.* **53:** 153, 1939	Infant	Male	0	13 days, from collapse	Adrenals hyperplastic.
54	Miller & Kenny: *Brit. J. Surg.* **27:** 728, 1940	10 yr.	Male	0	10, from postop. bleeding	Strong male libido. Operation for release of chordee.
55	Smith & Stockwell: *J. Urol.* **43:** 234, 1940	13 yr.	Female	13		Authors to try gonadotropic hormone later; familial, with Cases 56 and 57.
56	Smith & Stockwell: *Ibid.*	9 yr.	Female	9		See Case 55.
57	Smith & Stockwell: *Ibid.*	Infant	Female	Later		See Case 55.
58	Albert: *Brit. M. J.* **2:** 265, 1941	2 yr.	Female	0	2 years, of massive adrenal carcinoma	
59	Thelander & Cholffin: *J. Pediat.* **18:** 779, 1941	?	Female	0	Of adrenal insufficiency, age ?	Familial, with Case 60.
60	Thelander & Cholffin: *Ibid.*	5 wk.	Female	0	5 weeks, of adrenal insufficiency	See Case 59.
61	Werthemann: *Schweiz. med. Wchnschr.* **22:** 1335, 1941	12 wk.	Female	0		Sister of Case 62.
62	Werthemann: *Ibid.*	28 da.	Female	0		Sister of Case 61. Both patients had large adrenals.
63	Genitis & Bronstein: *J.A.M.A.* **119:** 704, 1942	10 yr.	Female	0		Changed to male at 10 years, without operation.
64	Genitis & Bronstein: *Ibid.*	4 yr.	Female	0		Adrenals hyperplastic with adenoma.
65	Kovacs: Bruns' *Beitr. z. klin. Chir.* **173:** 424, 1942	8 yr.	Female	0		Boyish.
66	McKenna *et al.*: *Tr. Am. A. Genito-Urin. Surgeons* **35:** 41, 1943	14 yr.	Female	0		Insufficiency after partial adrenalectomy. Sister had similar abnormality, as did 2 maternal aunts.
67	McKenna *et al.*: *Ibid.*	4½ yr.	Female	0		Partial right adrenalectomy for hyperplasia and cortical adenoma.
68	McKenna *et al.*: *Ibid.*	10 yr.	Female	0		Patient's desires were masculine, so was to be raised as a boy.
69	Rhodes: *Arch. Pediat.* **60:** 529, 1943	Infant	Female	0		Twin, of Case 70.
70	Rhodes: *Ibid.*	Infant	Female	0		See Case 69.
71	Engstrom *et al.*: *J. Clin. Endocrinol.* **4:** 152, 1944	?	?	0		No details.

TABLE 2.—*Continued*

No.	Author and reference	Age when seen	Environmental sex	Age at clitoridectomy (yrs.)	Age at death, and cause	Comment
72	Engstrom *et al.*: *Ibid.*	?	?	0		No details.
73	Engstrom *et al.*: *Ibid.*	?	?	0		No details.
74	McIntosh & Brown: *J. Pediat.* **27**: 323, 1945	5 yr.	Female	5		Estrogens helped feminization but closed epiphyses; familial, with Case 75.
75	McIntosh & Brown: *Ibid.*	6 yr.	Female	0	6 years; cause unknown	See Case 74.
76	Schnitman & Pesino: *Rev. Asoc. méd. argent.* **59**: 26, 1945	12 yr.	Female			Estrogens increased size of breasts and vagina.
77	Biggs & Rose: *J. Obst. & Gynaec. Brit. Emp.* **54**: 369, 1947	6 wk.	Female	0	6 weeks, from adrenal insufficiency	Called a female because bled from vulva at birth; familial, with Case 78.
78	Biggs & Rose: *Ibid.*	4 wk.	Male	0	4 weeks, from adrenal insufficiency	Had palpable prostate. Sister of Case 77.
79	Hain (Hernfield): *J. Path. & Bact.* **59**: 267, 1947	2½ yr.	Female	0		Two sisters aged 17 and 19 had same abnormality, one with adrenal cortical tumor.
80	Hain (Magill): *Ibid.*	3½ yr.	Female	0		Brother had adrenal cortical tumor.
81	Hain (McCall): *Ibid.*	2 yr.	Female			
82	Collier: *Am. J. Dis. Child.* **76**: 208, 1948	Infant	Female	0		No details; twin of Case 83.
83	Collier: *Ibid.*	Infant	Female	?		No details; see Case 82.
84	Whitelaw: *J. Clin. Endocrinol.* **8**: 583, 1948	5 yr.	Female	?		Abstract only.
85	Whitelaw: *Ibid.*	12 yr.	Male	0		Raised as male.
86	Zahn: *Schweiz. med. Wchnschr.* **78**: 480, 1948	Infant	Female	0	Infancy, from adrenal insufficiency	
87	Steiner & Barber: *Proc. Inst. Med., Chicago* **17**: 192, 1948	3 yr.	Female	0		Right adrenalectomy.
88	Steiner & Barber: *Ibid.*	18 mo.	Female	0		Left adrenalectomy.
89	Deming *et al.*: *J. Urol.* **61**: 144, 1949	Infant	Female	0	Infancy, from infection	
90	Deming *et al.*: *Ibid.*	Infant	Female	0	Infancy, from infection	
91	Hooks: *J. Urol.* **62**: 528, 1949.	?	Female	Later		Hypertrophied adrenals with insufficiency.
92	Hooks: *Ibid.*	?	Female	Later		Same as Case 91.
93	Carlgren: *Acta Paediatrica* **38**: 71, 1949	6 wk.	?	0	6 weeks, from adrenal insufficiency	Only child.
94	DeJong: *Maandschr. v. kindergeneesk.* **17**: 131, 1949	Infant	Female	0		Adrenal insufficiency.
95	Zuelzer & Blum: *J. Pediat.* **35**: 344, 1949	4½ mo.	Female	0	4½ months, from adrenal insufficiency	No effect from cortical extract.
96	Zuelzer & Blum: *Ibid.*	22 wk.	Male	0	22 weeks, from adrenal insufficiency	Sibling died with same syndrome.
97	Zuelzer & Blum: *Ibid.*	7 mo.	Male	0	7 months, from adrenal insufficiency	Sibling died at age of 4½ months, vomiting.
98	Melicow & Cahill: *J. Clin. Endocrinol.* **10**: 24, 1950	11 da.	Female	+		Progressive masculinization; to be raised as girl.
99	Melicow & Cahill: *Ibid.*	20 mo.	Female	+		To be raised as girl.
100	Melicow & Cahill: *Ibid.*	4½ yr.	Male	+		Although started as male, changed to female.
101	Melicow & Cahill: *Ibid.*	4½ yr.	Male	+		Changed from "environmental" male to female.
102	Stone & Zorgniotti: *Arch. Pediat.* **67**: 74, 1950	Infant	Female	0		Twin of Case 103.
103	Stone & Zorgniotti: *Ibid.*	Infant	Female	0		See Case 102.
104	Mazursky & Sawan: *J. Pediat.* **36**: 789, 1950	?	Female	0		Adrenal hyperplasia with insufficiency.
105	Hinman, Jr. (In press)	3 yr.	Female	0		Adrenal insufficiency; repair of hypospadias in order to raise as boy; sibling probably had adrenal insufficiency also.
106	Hinman, Jr.: *Ibid.*	3 yr.	Male	0		Adrenal insufficiency; to have hypospadias repair and be raised as male; sibling had similar genitalia and large adrenals.
107	Hinman, Jr. (Bentinck): (In press)	11 yr.	Female	3		Regrowth of clitoris. Sibling of Case 108.
108	Hinman, Jr. (Bentinck): (In press)	9 yr.	Female	½		Progressive masculinization. See Case 107.

the latter is devoted to younger children. Of the 53 reported cases, 14 were called boys either at birth or in early childhood. In the usual case there was indecision by the family and physician at birth, followed by a longer or shorter period of observation, and finally the conclusion that because of the development of the clitoris and other secondary sex characteristics, the child was a boy. Of these 14 patients, 2 developed in such a way that at or slightly before puberty the question of their correct sex was reopened and they thenceforward were considered to be girls. Later, one girl so changed became pregnant twice, and the comment was made that actually she was not at all masculinized. (We may question that this case was one of adrenal hyperplasia). Both of these girls underwent clitoridectomy, in order to conform with their new sex.

The remaining 39 were thought to be female at or soon after birth, usually in spite of the finding of overdeveloped genitalia. However, in 4 of these children, secondary sex changes became so marked by the age of puberty that the "environmental" sex was arbitrarily reversed. In only 1 of these cases (Young (2)) were plastic procedures carried out on the hypertrophied clitoris in an attempt to alter the sex anatomically. The comment recurs in the reports that these individuals were poorly adjusted physically, and consequently socially, to their environment.

Five of those patients raised as boys later married women, and 2 others, who became engaged to be married to women but were refused the marriage sacrament, committed suicide.

Of interest is the fact that the "males" waited longer before being seen by an interested physician (average age, 40 years); whereas the "females," perhaps because they found themselves less well adapted to their feminine role, consulted doctors earlier (average age, 30 years).

The incidence of clitoridectomy is of especial interest, since the procedure makes irrevocable the decision that the child become a girl, in the face of the progressive masculinization. Of the 53 patients over 15 years of age, most of whom had stayed out of the hands of doctors until this age, 17 underwent clitoridectomy; and, of these, all but 3 were operated upon after puberty, *i.e.*, after sexual trends were well established. In most of these cases, the decision seems to have been a wise one. However, among 101 patients reported on before puberty, 18 had had a clitoridectomy, and in all of these, the operation was performed before puberty. In 2, there was regrowth of the clitoris. It is of course difficult to determine in how many of these patients clitoridectomy was regretted in view of otherwise progressive masculinization.

Sixteen patients have been reported in whom partial adrenalectomy has been performed (Table 3). The results have been in general disappointing, since the adrenal tissue seems to regenerate, even though only very small

TABLE 3. EFFECT OF PARTIAL ADRENALECTOMY

Author and date	Pre- or post-puberty	Approximate amount of adrenal removed	Other treatment	Effect			17-ketosteroid excretion	Comment
				Hair	Voice	Physique		
Young 1937	Pre	⅓ of each	Preop. x-ray	No abnormal hair	Higher pitch	More feminine	No comment	Slightly improved
	Pre	⅓ of each	None	No change	No change	No change	No comment	No effect
	Post	⅓ of each	None	Softer	No change	Some mammary development	No comment	Patient felt improved
Broster *et al.* 1938	Post	Entire left	None	Softer	No further breaking	No change	No comment	Slight improvement
	Post	Entire left	None	—	—	—	No comment	Died postoperatively
	Post	Entire right	None	—	—	—	No comment	No comment
Dorfman 1940	Post	Entire left	Theelin*	No change	No change	Slight increase in size of breasts	Temporary decrease only	Made worse by treatment
Genitis 1942	Pre	"Partial"	None	—	—	—	No details	No details
	Post	"Partial"	None	—	—	—	No details	No details
Bayer 1947	Post	Right	—	No change	No change	No change	No details	"Disappointed"
Hain (Gemmell) 1947	Post	Entire left	Estrogen*	? No change	? No change	? No change	Temporary decrease only	No improvement
Wilhelm 1947	Post	1½ excised	Estrogen*	No change	No change	More feminine, with breasts	Decreased to 99 mg./24 hrs.	Better outlook
Steiner and Barber 1948	Pre	Entire right	None	No comment	No comment	No comment	No comment	No comment
	Pre	Entire left	None	No comment	No comment	No comment	No comment	No comment
Wilhelm 1950	Post	"Adrenalectomy"	None	Same	No comment	More feminine	No comment	Cyclic bleeding began
Hinman, Jr. 1950	Pre	Entire left	Estrogen*	Increased	No change	Increase in size of breasts	Decreased to 10 mg./24 hrs. temporarily	Effect not prolonged

* Note: In certain cases it is impossible to separate effects of administered estrogen from effects of adrenal resection; in general, the former may be said to have the greater effect.

amounts are left. In 6 cases the operation took place before puberty, whereas in the remaining 10 it was performed later. Although it has been suggested on theoretical grounds (Young) that better retardation of masculinization might be expected if the procedure were carried out before puberty, the results in clinical practice have not borne out this concept. This is especially true if decrease in 17-ketosteroid excretion is used as an objective measurement of improvement.

The effect of administered hormone can be seen in Table 4. Fourteen

cases are listed. Only 1 patient, excepting that of Wilkins (3) treated with cortisone, excreted significantly lower amounts of 17-ketosteroids. In general, estrogens may aid breast development or fill out the bodily contours, but they do not significantly alter the other masculine characteristics. In the patient reported by Wilkins, in whom 100 mg. of cortisone was given for fifteen days, there was a marked fall in the previously elevated 17-ketosteroid excretion (32–68 mg. per day) to normal levels (average, 6.5 mg. per day during the fifteen days of treatment). The action, however, lasted only during administration of the drug, for eleven days after cessation of therapy the titer had risen to 40 mg. per day. Additional patients have been treated by Wilkins and others (4) with consequent marked feminization. This result suggested the possibility that continuous small doses of cortisone orally might be effective in these patients—doses just sufficient

TABLE 4. EFFECT OF ADMINISTERED HORMONE

Author and date	Age of patient (yrs.)	Hormones administered	Results			Comment
			Hair	Voice	Physique	
Finkler 1934	16	Anterior pituitary hormone, with estrogen and progesterone	Decreased	Higher pitched	Increase in size of breasts	Good results only at first
O'Farrell 1935	19	Theelin and APL	Decreased	Slight improvement	Increase in size of breasts	Improved
Dorfman 1940	15	Theelin	No change	No change	Slight increase in size of breasts	Left adrenalectomy; made worse by treatment
McIntosh 1945	5	Stilbestrol	Increased axillary	No change	Decreased size of clitoris	Closed epiphyses
Schnitman 1945	12	Estrogen	0	0	Increase in size of breasts and vagina	Local improvement
Hain (Herzfeld) 1947	12½	Estrogen	0	0	Some breast development	No essential change, except menses
Hain (Gemmell) 1947	21	Estrogen	0	0	0	No comment
Wilhelm 1947	23	Estrogen	No change	0	More feminine	More alert; partial adrenalectomy
Deming 1949	23	Stilbestrol	No change	No change	No change	
Deming 1949	42	Stilbestrol, progynon and progesterone	No change	No change	Slightly more feminine	Lower 17-ketosteroid excretion
Wilkins 1950	15	Cortisone, 100 mg. for 15 days	No comment	No comment	No comment	Marked fall in 17-ketosteroid excretion, lasting 11 days
Hinman, Jr. 1950	18	Ethinyl estradiol, stilbestrol and premarin	Increased	No change	Increase in breast development	Hirsutism is greatest problem
		Cortisone, 25 mg. daily	Slightly decreased	No change	No change	Period of administration too short
Hinman, Jr. (Bentinck) 1950	9	Cortisone, 25 mg. daily				Period of administration too short
Hinman, Jr. (Bentinck) 1950	11	Cortisone, 25 mg. daily				Period of administration too short

to depress pituitary ACTH secretion without getting side effects resembling Cushing's syndrome. This approach offers an alternative method of treatment, especially in children already raised as girls.

SUMMARY AND CONCLUSIONS

1. In order to obtain a rationale for surgical sex reversal in clinical practice, case reports of 149 patients with female pseudohermaphrodism due to fetal adrenal cortical hyperplasia have been reviewed and tabulated, with the inclusion of 5 new cases.

2. The masculinization in female pseudohermaphrodism is usually progressive. The progression can be detected in childhood by increased bone age, advanced secondary sex characteristics and elevated 17-ketosteroid excretion.

3. Of 53 patients over 15 years of age, 14 were considered to be male at birth but 2 were later "feminized" by clitoridectomy. The remaining 39 were reared as females, but 4 became so masculinized that it was later decided to regard them as males. Many of the others were adjusted poorly to their environment because of their masculine physical characteristics.

4. Since clitoridectomy is irreversible, it perhaps had best be reserved until puberty for patients with feminine inclinations but without progressive masculinization, or for patients who will take suppressive doses of cortisone indefinitely.

5. The decision as to sex in these individuals should rest on the degree and progression or suppression of masculinization, since social and psychologic sex patterns will follow the arbitrary "environmental" sex.

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THE TREATMENT OF ADOLESCENT ACNE WITH TOPICAL APPLICATION OF ESTROGENS*†

M. JAMES WHITELAW, M.D.

Phoenix, Arizona

ACNE vulgaris stands near the top of the list as one of the most common skin conditions seen by either the dermatologist or the general practitioner (1). Various authorities have estimated that it comprises approximately 15 per cent of all skin diseases (2, 3) and as such deserves our special attention. It is noted predominantly at adolescence (4). It is especially during this period that the boy or girl is psychologically least prepared for the disfigurement that this disease may bring. If the pathologic process is allowed to proceed, irreparable damage may be produced, not only to the skin but also as far as social adjustment is concerned.

Although roentgen therapy is said to offer approximately an 80 per cent "cure," many dermatologists feel that it is contraindicated before the age of 17. There have been numerous advocates of elimination diets, each author having his particular ideas as to what to avoid (5, 6, 7). The only other recognized medical management has been the use of kerolytic agents and the removal of the plugs from the follicular orifices (8). Some authorities feel still that the results in the treatment of acne continue to be somewhat discouraging.

Because of the fact that in recent years the relationship between sex hormones, gonadotropins and acne has been brought to the fore by Bloch (9), it was decided as early as 1941 to investigate the effects of topical application of estrogens[1] in adolescent acne.

MATERIAL

All the patients in this series were unselected. Studies were carried out by the author in New York, Dallas, and Phoenix, and included both private and clinic patients. Only those patients who were treated and observed for a period of six or more months were included in this study. Seventy-six

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[1] The estrogenic preparation used was Premarin Cream which was supplied through the kindness of Ayerst, McKenna & Harrison, Ltd.

were males who ranged in age from 13 to 18 years, and 23 were females aged 13 to 19. No dietary restrictions were imposed. The patients were instructed to wash their faces mornings and evenings and to apply the preparation, rubbing it in well. A jar containing 52 grams of a conjugated estrogen in a non-greasy base was supplied, each gram of the ointment containing estrogenic activity equivalent to 0.625 mg. of sodium estrone sulfate. The contents of the jar lasted from twenty-eight to thirty days, so that approximately 1.25 mg. of the estrogen was applied daily. No other therapy was employed during the time that these patients were being treated. During the earlier phase of the investigation, urinary hormonal levels of estrogens and 17-ketosteroids were obtained, but because of lack of facilities in the recent past this aspect of the study was given up.

RESULTS

In 65 of the 76 male patients, within two weeks of institution of therapy, there was a definite and marked change in the texture of the skin. This consisted of softening, and a slight decrease in the oiliness and hyperkeratosis. There was also some evidence of a decrease in sebaceous gland activity, as well as a paling of the rosacea-like appearance around the acneform lesions. After six months of therapy, 55 per cent of the cases showed a marked improvement, 21 per cent showed moderate improvement, and in 24 per cent there was no change (Figs. 1–6). In only 1 case was there an accentuation of the acne while under treatment. Though there was far more exposure to actinic rays in the group treated in Phoenix, this factor did not appear to have any influence on our results. Careful interrogation revealed no decrease in libido in any of the boys in the older age group. Examination of the testes showed no evidence of either softening or decrease in size. Examination of the spermatozoa in 3 patients before, during, and after therapy revealed no change in number, morphology, or motility. No gynecomastia was noted, nor was there any apparent influence on the body or genital hair. In the series of 23 girls, 21 per cent showed satisfactory response within a period of six months and 12 per cent showed some improvement. Sixty-seven per cent failed to respond, and of this group,26 per cent showed mild accentuation of their comedones. No influence on the menstrual cycle was observed.

DISCUSSION

It has been known for years that in both the male and female, overproduction of androgens, due to hyperactivity of the adrenal from pituitary stimulation, from hyperplasia, or from a tumor, could produce definite comedones (10). Masculinizing neoplasms of the ovary also had this effect.

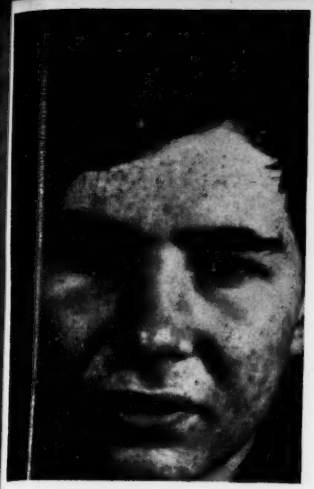

FIGURE 1

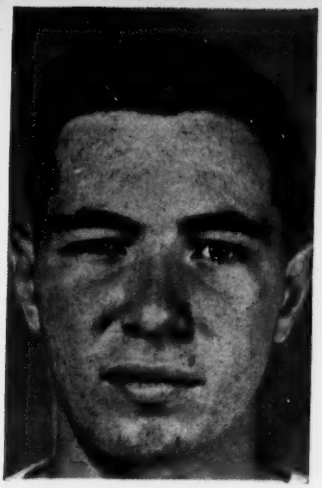

FIGURE 2

FIG. 1. Case 32, D.F., 15 years old, with moderately severe acne vulgaris previous to therapy.

FIG. 2. Same patient, five months after starting therapy.

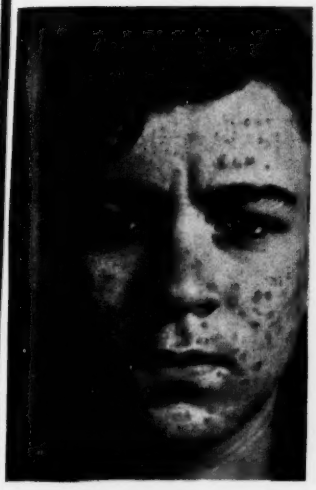

FIGURE 3

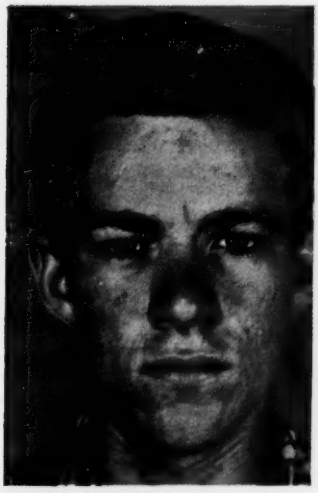

FIGURE 4

FIG. 3. Case 38, G.S., 16 years old, with severe acne previous to treatment.

FIG. 4. Same patient, four months after institution of therapy.

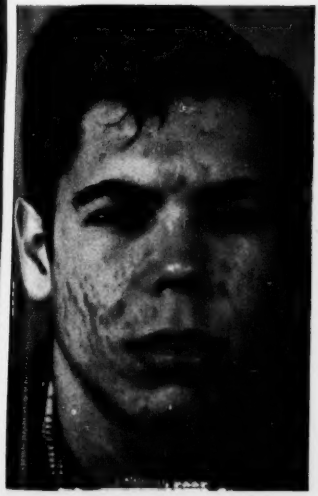

FIGURE 5

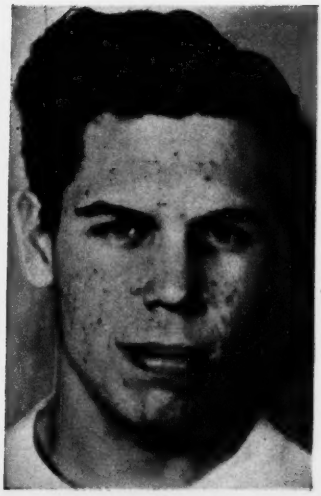

FIGURE 6

FIG. 5. Case 47, N.H., 17 years old, with severe acne before therapy.

FIG. 6. Same patient, nine months after institution of therapy.

Conversely, it was noted in the literature that in eunuchoid males acne was never seen. In this group, when testosterone was given, oiliness was first observed, followed by acneform lesions produced about the nose (11). In the last year, since potent adrenal cortical preparations have been available, several authors have reported on the production of typical comedones after induction of hyperadrenalcorticism by cortisone (12) or ACTH (13).

In 1939 Hollander and Schmitt (14) first treated 41 females and 19 males with an oral water-soluble estrogenic extract and reported some improvement following two months of therapy. Barber (15) in a review of the influence of sex hormones on the skin, believed that the agent responsible for acne vulgaris was the male hormone. Lawrence and Werthessen (16) reported a decrease in the urinary estrogen excretion with a definite androgenic preponderance. They concluded that comedones in acne were the result of an increase in the androgen-estrogen ratio. Fifteen of their 25 patients became acne-free after periods of treatments with ethinylestradiol or diethylstilbestrol varying from two to six months. Shapiro (17), using topical estrogens in 30 resistant cases of acne, was able to induce a remission in two thirds of the patients in whom treatment was a failure under classic management. Way and Andrews (18) obtained a 50 per cent, fair, response to subcutaneous injections of estrogens or progesterone, with a 25 per cent recurrence. Goeckerman (19) in 26 selected cases followed over a period of eight years reported varying success, using both parenteral and oral estrogens.

It would appear from our results that, in the average male, the topical application of estrogens to the skin of the face may either nullify the effects of the excessive circulating androgens or at least decrease their influence. Undoubtedly there is a difference in the threshold response of the skin of various individuals to the same titer of circulating androgens. In the male, one third of the total circulating androgen is testicular in origin, whereas in the female it is presumably all from the adrenal. It is on this basis, perhaps, that the difference in our results between the male and the female can be best explained. It has been shown (20) that in order to depress the 17-ketosteroid output of female pseudohermaphrodites, enormous quantities of estrogens must be utilized. In the male, however, it has been noted that small quantities of estrogens may depress both interstitial and tubal function. It may be that in the adolescent girl the amount of estrogen necessary to nullify the effects of the circulating adrenal androgen on the end organ, the skin, is very high. It is conceivable that during this period of life there is a marked disturbance in LH production which could possibly alter the adrenal androgenic output (21). It is recognized that our female series is rather small and that a much larger group is necessary be-

fore definite conclusions can be reached. In the adolescent male, however, the beneficial results are clear cut, and topical estrogen therapy deserves a place in our armamentarium.

SUMMARY

During the past six years, 72 cases of typical adolescent acne in males ranging in age from 13 to 18, were treated by inunction of conjugated estrogenic substances in a non-greasy base, using an amount of estrogen approximately equivalent in activity to 1.25 mg. of sodium estrone sulfate daily. Within fourteen days, a marked improvement in skin texture and tone was noted in 90 per cent of those treated. In patients treated six months or longer, 55 per cent showed marked improvement, 21 per cent showed slight improvement, and 24 per cent failed to respond. In only 1 instance were the lesions exaggerated. In a series of 23 girls, ranging in age from 13 to 19 who received the same treatment, only 21 per cent responded satisfactorily and 12 per cent showed moderate improvement. In both series no other form of therapy or diet was used during the test period. There was no evidence in the adolescent male of any deleterious effects from the inunction of estrogenic hormones in the dosage used.

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THE SCINTILLATION COUNTER IN CLINICAL STUDIES OF HUMAN THYROID PHYSIOLOGY USING I^{131}*

HERBERT C. ALLEN, JR., M.D.,† RAYMOND L. LIBBY, PH.D. AND BENEDICT CASSEN, PH.D.

Radioisotope Laboratory, Wadsworth General Hospital, Veterans Administration Center, and the Departments of Radiology and Biophysics, School of Medicine, University of California, Los Angeles, California

DIRECTIONAL and wide-angle scintillation counters have been employed in various clinical studies of human thyroid physiology using eight-day radioiodine. These studies have evolved the precise delineation of the area covered by the thyroid and measurements of the rate of uptake and the total uptake of I^{131} by the thyroid gland, using doses of 10 microcuries. These studies have been possible because the scintillation counters employed are more efficient detectors of the gamma radiation from eight-day radioiodine than the Geiger-Müller tubes now in general use. Even specially designed Geiger tubes respond to about 2 per cent of the total gamma ray emission from a radioactive source (1). Thus, up until this time the intrinsic insensitivity of the Geiger-Müller tube has limited progress in the in vivo studies of thyroid physiology and therapy in human beings.

Ever since Hertz (2) first used radioiodine for therapy in human beings in 1942, a number of important problems in this field have lacked definitive answers. The most important of these is a precise determination of the ionizing radiation delivered to the thyroid, in order to evaluate this method of therapy properly. Any calculation of total irradiation involves a knowledge of the total weight of the gland, the total amount of radioiodine present in the gland, its distribution within the gland and its biologic half-life. Of these factors, only the total amount of radioiodine present and its biologic half-life can be measured with any degree of accuracy with detecting equipment now commonly employed, and then only if rela-

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† Present address: Veterans Administration Hospital, and Baylor University College of Medicine, Houston, Texas.

tively large tracer doses of 50 microcuries or more of I^{131} are administered.

At the present time there are no accurate methods of estimating thyroid size other than manual palpation of the gland. From this, combined with clinical judgment, an estimation of its weight is made. Soley (3) and his colleagues estimated thyroid weights by this method for some twelve years. In only 25 per cent of 74 cases examined prior to thyroidectomy were they able to estimate within ± 10 per cent of the weight of the gland, and errors as high as 42 per cent were observed.

Concerning the estimation of the distribution of radioiodine within the gland, no equipment has been available to study this problem in vivo, so that therapeutic dosage has been calculated on the assumption of a uniform distribution of radioiodine throughout. Our own in vivo studies with the directional scintillation counters and radioautographs of sections of glands indicate that this is not the case.

A second challenge that has not been overcome and has limited the universal acceptance of radioisotopes in diagnosis, as opposed to therapy, has been the inability to use small, relatively harmless tracer doses. It is generally recognized from the numerous in vivo studies that have been published that radioiodine offers a diagnostic tool for studying thyroid metabolism. However, its use as such has been limited because of the comparatively large tracer doses, of the order of 50 to 250 microcuries, that have to be used because of the insensitivity of Geiger tubes as detectors of gamma radiation. This objection can be largely dispelled if small tracer doses of the order of 1 to 10 microcuries are used. Our results indicate that the substitution of scintillation counters for Geiger-Müller counters will permit the use of these small amounts of radioiodine for in vivo studies of total uptake or rate of uptake of inorganic iodine by the thyroid gland.

Several reports (4, 5, 6, 7) have appeared in the literature on the use of photomultiplier tubes for the detection of scintillations produced by gamma radiation in various phosphors such as calcium tungstate and anthracene. Our investigation is concerned with clinical studies of thyroid physiology in human beings in which two different types of scintillation detectors have been employed. The first type is a directional scintillation gamma ray detector[1] (7) designed principally for the delineation of areas of radioactivity; the second is a wide-angle scintillation gamma ray detector designed for thyroid uptake studies utilizing small tracer doses of I^{131}.

Two directional scintillation counters have been employed in these studies. One of these directional scintillation counters has an iodine gamma ray sensitivity about 15 times per unit area compared to that of a con-

[1] Developed under Contract AT-04-1-Gen-12 between the Atomic Energy Commission and the University of California at Los Angeles.

ventional end-window Geiger tube; the other has a sensitivity factor of 27 times. This increased sensitivity permits the use of limiting apertures of one-quarter inch or less in these counters. Thus, when the counter is placed in close proximity to the radioactive source, the angle at which the gamma radiation enters the tube is restricted to approximately that of the aperture. This small angle greatly increases the resolving power of the counter. Thus, it becomes relatively easy to delineate in vivo the margins of the lobes of the thyroid after the administration of tracer doses of I^{131} of the order of 100 to 200 microcuries. It is also possible to locate within the gland itself small areas of both low and high activity and to delineate functioning metastatic thyroid nodules. If a careful in vivo survey is made of the general area occupied by the thyroid gland, it is possible to outline both a frontal and a lateral silhouette of the gland that represents within a few millimeters the area occupied by the gland itself. Based on measurements of the frontal and lateral profiles thus obtained, calculations can be made to determine the total volume of the thyroid gland. The details of these determinations will be presented in a subsequent report.

A wide-angle scintillation counter of design different from the directional scintillation counter has been used for uptake studies of I^{131} by the thyroid gland. The wide-angle scintillation counter has the advantage of greatly increased sensitivity to the gamma rays from 8-day radioiodine, of the order of 94 times as compared to the conventional Geiger-Müller tube. Thus, even though its utility is in many respects essentially similar to conventional detecting equipment, it will permit the use of smaller tracer doses of from 1 to 10 microcuries of I^{131} in clinical studies of thyroid physiology, such as the rate and total uptake of inorganic iodine.

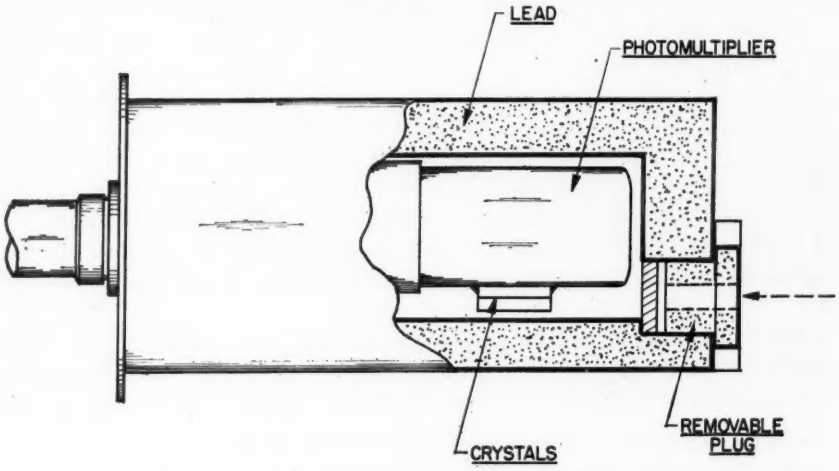

FIG. 1. Schematic drawing of directional scintillation counter (7).

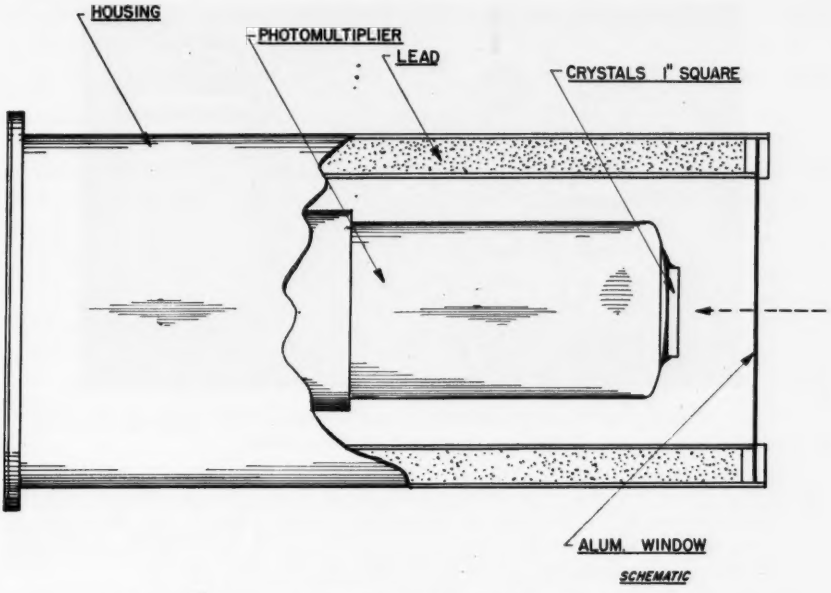

FIG. 2. Schematic drawing of wide-angle scintillation counter.

SCINTILLATION COUNTERS AND ACCESSORY EQUIPMENT

Description of directional scintillation counter: Figure 1 is a schematic longitudinal drawing of the directional scintillation counter (7). The sensitive scintillating element is made up of four $\frac{3}{4}$ by $\frac{1}{8}$ by $\frac{1}{8}$" square polished rods of calcium tungstate cemented together with Canada balsam, giving a detecting crystal approximately $\frac{3}{4}$" long and $\frac{1}{4}$" wide. This crystal, in turn, is cemented onto the glass envelope of a 1P21 type photomultiplier tube, opposite the lower two-thirds of the window to the photo cathode. The crystal is then wrapped with a strip of aluminum foil to aid in reflecting light back into the photomultiplier tube.

The photomultiplier tube, and the resistors provided to give the correct operating potentials, are enclosed in a lead-lined, chromium-plated brass housing $3\frac{1}{4}$" in diameter and 6" long, weighing 9 pounds. Thirteen millimeters of lead shielding are used on the sides and 17.5 millimeters of lead over the operational end of the housing. This shielding is sufficient to reduce the intensity of the gamma radiation from I^{131} to less than 5 per cent on the sides and less than 2 per cent on the end. When additional shielding is required, a sleeve with $\frac{1}{2}$" of lead on the bottom, having a $\frac{1}{4}$" or larger port, can be slipped over the end of the housing (not shown in drawing). Three removable lead plugs which fit into the face of the housing, as shown, have been used. In addition, a solid lead plug is used to obtain background readings. One of the plugs has a 0.250 inch aperture; the other two plugs have $6\frac{1}{2}°$, and 10° tapers and apertures of 0.200 and 0.380 inches respectively (Fig. 3).

Description of wide-angle scintillation counter: Figure 2 is a schematic longitudinal drawing of the wide-angle scintillation counter. The sensitive scintillating element is made up of eight 1 by $\frac{1}{8}$ by $\frac{1}{8}$" polished rods of calcium tungstate cemented together to provide a 1 by 1 by $\frac{1}{8}$" detector. This crystal, in turn, is cemented to the center of the

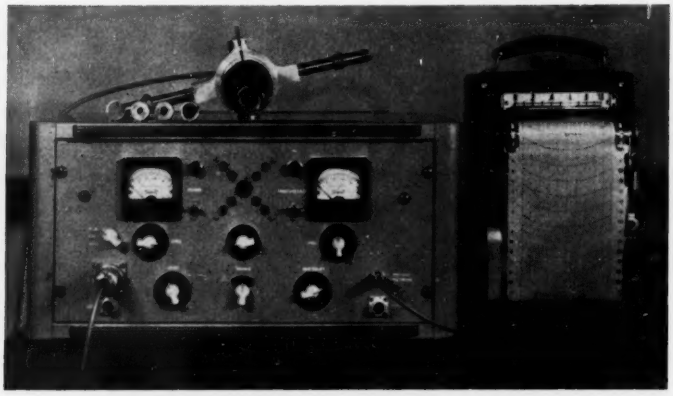

FIG. 3. Directional scintillation counter, rate meter circuit and Esterline-Angus automatic recorder.

photosensitive surface of a Type 5819 photomultiplier tube. The lead-lined housing has a wall thickness of 9.5 millimeters. A light-tight window of aluminum, 173 milligrams per square centimeter, is cemented onto the end of the lead housing. Figure 4 is a photograph of the wide-angle scintillation counter, and accessory equipment.

Description of accessory equipment: The signal from the scintillation counters is fed into a counting rate meter and recorded on a 1 milliampere Esterline-Angus automatic

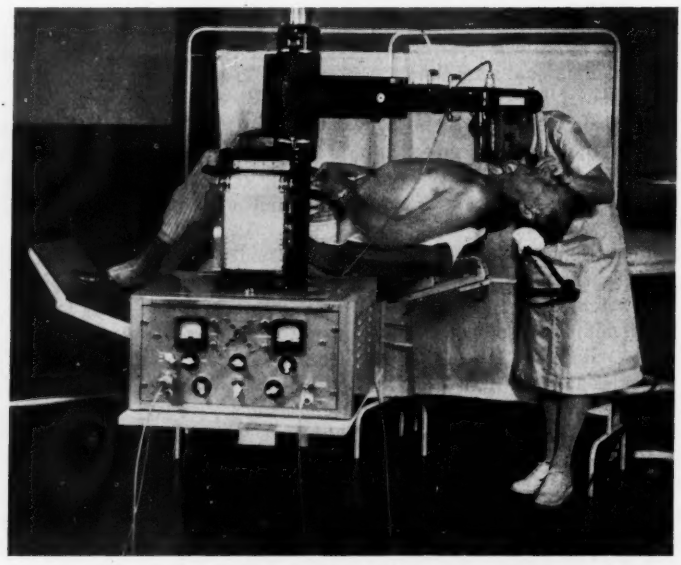

FIG. 4. Operational set-up with wide-angle scintillation counter and patient lying on dental chair.

recorder. The rate meter is provided with a selector switch so that any one of six time constants varying from 0.01 second to 5 seconds may be used to obtain optimal recording conditions. Three counting ranges are provided so that 10, 100 and 1,000 counts per second may be recorded at full scale deflection of the recording milliameter.

Operational set-up for in vivo measurements: Figure 4 shows the clinical application of the wide-angle scintillation counter as it is employed for the measurement of iodine uptake in patients. As shown, the scintillation counter is mounted on a portable x-ray stand which permits a maximum of versatility in angulation of the counter. The patient sits or lies on a sponge rubber mattress placed on a dental chair. This arrangement has been found to be exceedingly helpful and time-saving in that it is possible to move either or both the scintillation counter and the patient with minimum effort. For example, in determining the uptake of I^{131} by the thyroid where it may be desirable to obtain measurements at several different distances from gland to the tube, it has been found more convenient to center the scintillation counter carefully over the thyroid, lock it in this position, and then move the patient to the desired distances by means of the hydraulic lift provided on the dental chair. This lift permits a smooth and precise up and down motion.

Comparative sensitivity of end-window Geiger-Müller counter, directional scintillation counter, and wide-angle scintillation counter: Because of the extreme differences in geometry between the end-window Geiger-Müller tube and the directional scintillation counter, the comparative sensitivity of the two gamma-ray detecting devices could be checked only by restricting the gamma-ray source to a very narrow beam. This was accomplished by placing the iodine source directly under a $\frac{1}{8}''$ hole in the top of a $2''$ lead chamber which completely surrounded the source. The distance from the $\frac{1}{8}''$ opening to the geometric center of the Geiger-Müller tube and to the center of the calcium tungstate crystal was identical. Beta particles from the iodine source were eliminated by an appropriate aluminum filter. The total number of counts observed for both counters was such that the counting error was less than 1 per cent. The ratio of the net count for one directional scintillation counter to the net count observed for the Geiger-Müller tube was 15.2; for the second directional scintillation counter the ratio of the counts was 26.8. The increased sensitivity for the second directional scintillation counter, as compared to the first one, over the end-window Geiger-Müller tube is probably due to differences in the response of the 1P21 photomultiplier tube.

The wide-angle scintillation counter has an increased sensitivity to the gamma rays from I^{131} of 94 times that of the end-window Geiger-Müller tube. This comparative efficiency of the two counters in detecting gamma radiation from radioiodine was determined under comparable geometric conditions. A source of radioiodine was placed equidistant from the crystal of the wide-angle scintillation counter and from the mica window of the end-window Geiger-Müller tube and the counts per second recorded for each instrument. Beta particles from the radioiodine source were elimi-

nated by means of copper filters. The distance from the source to counter in each instance was such that all of the radioactive material was covered by the solid angle subtended by the counters. A similar comparison was also made between the two counters on the I^{131} radioactive thyroids of 2 patients. The ratio of the net counts per second for each instrument indicated that the wide-angle scintillation counter recorded 94 times more counts than the end-window Geiger-Müller tube.

CLINICAL APPLICATION OF THE DIRECTIONAL SCINTILLATION COUNTER

Delineation of the thyroid by means of the directional scintillation counter: Our first attempts to approximate the size of the thyroid were made by determining the thyroid-to-counter distance at which the gland effectively became a point source. Knowing the solid angle subtended by the counter at this distance, it is possible to outline a circle which approximates the general area covered by the thyroid. This crude approximation of the size of the gland has many serious objections. It is obvious that the gland is not circular, and in many instances the two lobes are asymmetric. A thyroid with a large asymmetric lobe measured by this method gives an entirely erroneous impression of the overall size of the gland.

The method currently in use clinically for delineating the thyroid gland involves the determination of a series of "isocount" points which represent the outer margins of the lobes of the thyroid and the isthmus.

The essential techniques were developed first on thyroids removed at autopsy from patients who had received radioiodine. These specimens included the entire thyroid gland, the overlying strap muscles, the thyroid and cricoid cartilages, the larynx, the trachea and the esophagus. The glands were exposed by careful dissection and removal of the overlying subcutaneous tissue and the sternothyroid and sternocricoid muscles. The thyroid gland and accompanying structures were placed horizontally in the dental chair and oriented so that they approximated the same position as that of the thyroid of a patient lying supine. A $\frac{1}{8}''$-thick transparent lucite drawing board (Fig. 5) was supported 5 to 6 millimeters above the gland. On this was mounted a transparent sheet of cellophane on which were drawn perpendicular coordinate guide lines, forming $\frac{1}{4}''$ squares. For the purpose of identification, the ordinates and abscissae were labeled. The middle ordinate line was placed directly over the midsagittal line of the trachea so that it bisected the horizontal axis of the isthmus and the notch of the thyroid cartilage.

The directional scintillation counter mounted on the portable x-ray stand was moved into position, 1 to 2 millimeters above the cellophane. This fixed distance was maintained throughout the survey and no attempt was made to maintain a constant thyroid-to-counter distance. The scin-

tillation tube was moved in a horizontal plane over each of the transverse grid lines and 15 to 60-second counts, depending on the level of radioactivity, were recorded at each intersection. The counts per second for each intersection were recorded on an automatic recording Esterline-Angus milliameter. The counting rate for 75 to 125 points was thus obtained. The time

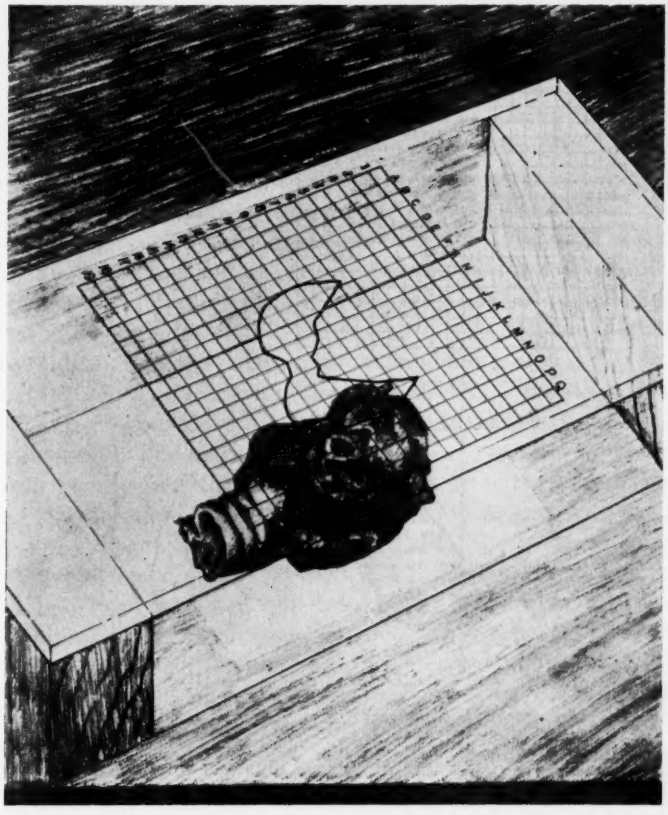

FIG. 5. Schematic drawing of the experimental layout employed to prepare frontal silhouettes of radioactive autopsy thyroids.

required for a complete mapping of the thyroid was approximately one to one and a half hours.

After the completion of the survey, the counts per second were transcribed from the Esterline-Angus recorder to the cellophane grid (Fig. 6A). The background in counts per second for nonthyroid tissue in the general region immediately adjacent to the thyroid gland was represented by the

counts obtained from the points near the periphery. The average counts per second for these peripheral points were subtracted from each of the points previously recorded (Fig. 6B). In some, the average nonthyroid background was obtained by averaging the series of counts per second recorded for the midsagittal line, exclusive of those representing the thy-

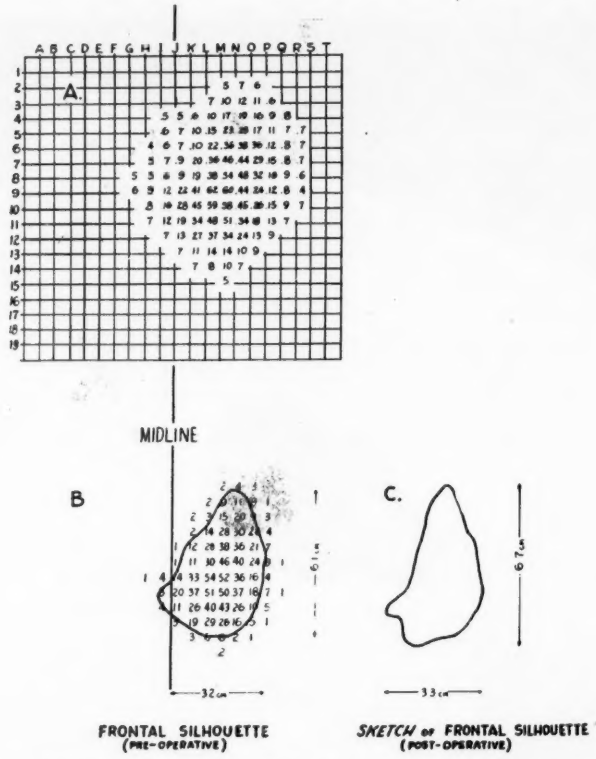

FIG. 6. A. Plot of the net counts per second obtained from the frontal survey of a patient's thyroid. B. Plot of the counts per second minus the nonthyroid background and the frontal silhouette drawn from these counts. C. Sketch of the frontal silhouette obtained postoperatively. The calculated preoperative and the actual postoperative dimensions of the gland are shown.

roid isthmus. It was felt that this latter determination was more representative of the actual background existing several millimeters from the margin of the lobes of the thyroid. The remaining series of points in counts per second, after subtracting nonthyroid background, essentially represent radioactivity originating from the thyroid gland itself and delineate the frontal silhouette of the isthmus and each lobe. The margins of the gland

were obtained by drawing lines between the peripheral "isocounts." Figure 5 shows a thyroid obtained at autopsy, and the silhouette of this thyroid as obtained with the directional scintillation counter equipped with a $\frac{1}{4}''$ aperture.

Six autopsy specimens of radioactive thyroids were mapped as described and it was found that the delineation checked within 1 to 3 millimeters of the actual size of the gland as measured independently with calipers. The same degree of accuracy in delineating the gland could be obtained by independent analyses of the recorded counts by persons who were unfamiliar with the size and shape of the gland.

Using the same technique of determining the "isocount" points, as previously described, the right and left lateral silhouettes of the gland were obtained. These were made by turning the thyroid gland and accompanying structures on its side in such a manner that first the right and then the left lobes lay directly beneath the lucite drawing board and cellophane.

This technique of mapping the thyroid gland has been applied clinically on a total of 14 patients, 6 with carcinoma of the thyroid, 7 with diffuse hyperthyroidism, and one with a nontoxic nodular goiter.

In most instances, in these in vivo studies designed to outline the thyroid gland, an intravenous dose of 100 to 200 microcuries of carrier-free I^{131} was administered. The mapping of the gland was usually done at various times from twenty-four to seventy-two hours after the administration of the dose. The directional scintillation counter was mounted on the arm of a portable x-ray stand, as previously described. The patients were placed in a dental chair or on a conventional E.E.N.T. operating table, the back of which had been adjusted and lowered to the horizontal position. A 2-inch-thick foam rubber mattress was used on the dental chair to insure comfort. The patient's head was slightly extended so that the skin of the neck was horizontal (Fig. 4). The transparent lucite drawing board, cut to conform to the contour of the structures of the submental region, was placed horizontally over the neck, resting on the sternum and the thyroid cartilage. It was then fixed in this position with Scotch tape. The cellophane was then placed on the lucite board and positioned so that the middle ordinate line was superimposed over a line previously drawn on the patient's skin from the center of the notch of the thyroid cartilage to the center of the suprasternal notch. The suprasternal notch, the notch of the thyroid cartilage and the lateral borders of the patient's neck were sketched on the cellophane with a china marking pencil. The exact location of the notch of the thyroid cartilage is important. It is later used as a reference point for indicating areas of radioactivity either within the thyroid gland or in the neck of totally thyroidectomized patients suffering from thyroid carcinoma. These areas can then be projected onto the patient's neck,

which is visible through the cellophane and lucite, and the exact area of activity marked on the skin.

The "isocount" points were determined and the frontal and lateral silhouettes were drawn in the same manner as described above for the in vitro mapping of autopsy specimens of thyroid glands.

In 2 of the 14 cases studied thus far we have been fortunate in obtaining measurements of the gland in situ and immediately following surgical removal. One of these patients had carcinoma of the thyroid and had had a previous right hemithyroidectomy. A dose of 500 microcuries of carrier-free I^{131} was given orally and frontal and lateral silhouettes of the remaining left lobe were made forty-eight hours later (Figs. 6 and 7). Measurements obtained from these "isocount" silhouettes indicated a lobe of 6.1 by

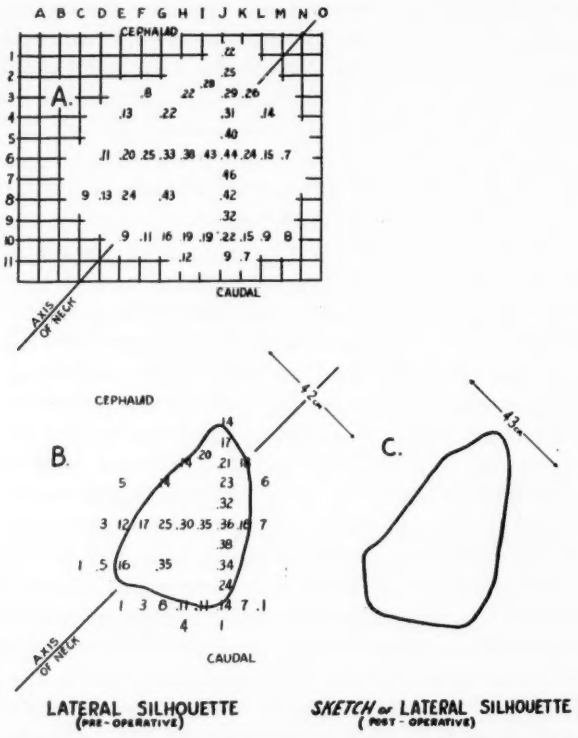

FIG. 7. A. Plot of the net counts per second obtained from the lateral survey of a patient's thyroid. B. Plot of the counts per second minus the nonthyroid background and the lateral silhouette drawn from these counts. C. Sketch of the lateral silhouette obtained postoperatively. The calculated preoperative and the actual postoperative dimensions of the gland are shown.

3.3 by 4.2 cm. in size (Figs. 6B and 7B). The actual size of the lobe measured in vivo at the time of surgery was 6.7 by 3.3 by 4.3 cm. (Figs. 6C and 7C).

In another case of nontoxic nodular goiter, the silhouette of the right lobe obtained with the directional scintillation counter measured 5.2 by 3.3 by 3.2 cm. The dimensions obtained immediately following surgical removal showed the right lobe to measure 5 by 3.2 by 3.2 cm. These 2 cases serve to show the accuracy with which the size of the thyroid may be predicted by in vivo mapping with the directional scintillation counter. Three other cases in which the thyroid gland or residual areas of radioactivity were outlined are shown in Figure 8. In Figure 8C, it is not known what these areas of radioactivity represent, whether they are residual normal thyroid tissue remaining after total thyroidectomy or are carcinomatous thyroid functioning tissue. In this particular case it was possible to outline

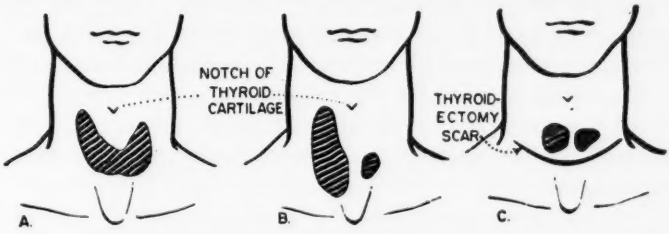

FIG. 8. A. The frontal silhouette obtained from an asymmetrical thyroid. B. Frontal silhouette obtained after a subtotal thyroidectomy for hyperthyroidism. C. Frontal silhouettes of radioactive tissue remaining after total thyroidectomy for carcinoma.

radioactive areas measuring as little as 0.9 by 1.0 cm., even though they were less than 1.5 cm. apart. Figure 6A shows the silhouette as outlined with the directional scintillation counter of an asymmetrical thyroid gland in one of the cases of hyperthyroidism studied. This silhouette was obtained on three separate occasions. The last one was done eight weeks after the administration of 5.29 millicuries of I^{131}.

It is obvious that it is desirable to obtain additional surgical confirmation of the predicted size of the thyroid gland and other areas of radioactivity made from in vivo measurements with the directional scintillation counter. However, the accuracy with which the size of the thyroid could be determined on the 6 autopsy specimens and the 2 cases confirmed at surgery warrants the feeling that a rather precise delineation can be made on patients. To make comparable measurements, it is desirable that the glands be measured in situ prior to surgical removal, to obviate the decrease in size that takes place following excision due to manipulation and blood loss.

Our experience to date in outlining in vivo and in vitro thyroid glands indicates that activities of 0.5 to 1.0 microcurie per gram of tissue are required to obtain satisfactory delineation. This would preclude the use of small doses of radioiodine of the order of 10 microcuries that are routinely employed in thyroid uptake studies if mapping of the gland is desired.

Determination of the uptake of I^{131} with the directional scintillation counter: The directional scintillation counter has been used to determine the per cent of the administered dose of I^{131} that is taken up by the thyroid gland, using conventional tracer doses of 50 to 250 microcuries. It has been applied in 123 such studies in which consecutive determinations were also made, using an end-window Geiger-Müller tube. The experimental details and the comparative results between the two detecting instruments will be given in a subsequent report.

In general, the uptake studies with the directional scintillation counter were carried out with an aperture of 1.9 centimeters, with the counter 20 to 50 centimeters from either the administered dose or from the thyroid gland. These distances were picked on the assumption that the solid angle or cone of activity covered by the calcium tungstate crystal should encompass the area occupied by the thyroid gland. Tracer doses of from 50 to 100 microcuries are required to insure reliable uptake determinations with this counter.

APPLICATION OF THE WIDE-ANGLE SCINTILLATION COUNTER IN I^{131} UPTAKE STUDIES USING TRACER DOSES OF 10 TO 20 MICROCURIES

Up to the present time the literature indicates that tracer doses of I^{131} ranging from 50 to 250 microcuries are being used in clinical studies of thyroid physiology and metabolism. The major factor precluding the use of smaller tracer doses is the inherent insensitivity of the Geiger-Müller tube to gamma radiation. Even especially designed Geiger tubes respond to only 1–2 per cent of the total gamma ray emission (1).

Before radioiodine uptake studies can be accepted as a routine diagnostic hospital procedure for studying thyroid function of all types of patients, the dosage must be such that no permanent radiation damage to any organ can reasonably be expected. Therefore, if present tracer dosage levels of 50 to 250 microcuries can be reduced to 1 to 10 microcuries in thyroid uptake studies, a considerable advance will have been made in removing one of the most serious objections to its acceptance as a routine hospital procedure.

Table 1 shows a comparison of the roentgen dosage delivered to a patient's skin from various common x-ray laboratory procedures and the equivalent roentgens (e.r.) delivered to hypo-, eu- and hyper-thyroid

TABLE 1. COMPARISON OF ROENTGEN DOSAGE FROM VARIOUS X-RAY PROCEDURES AND THE EQUIVALENT ROENTGENS DELIVERED TO THE THYROID FROM A DOSE OF 10 MICROCURIES OF I^{131}

	Type of patient			X-ray procedure		
	Hypo-thyroid	Euthy-roid	Hyper-thyroid	Routine GI series	Average lumbar spine	Average gall bladder study
Weight of thyroid gland	25 Gm.	25 Gm.	35 Gm.			
Calculated % uptake I^{131}	10%	25%	60%			
Microcuries/Gm.	0.04	0.1	0.17			
Thyroid dose in e.r.*	5.6	14.0	23.8			
R exposure to skin from x-ray**				40.0	13.3	5.5

* Assumptions made: 140 e.r. per μc. I^{131} per gram, 8-day biologic half-life.

** Assumptions made: generally accepted x-ray procedures used on average-size patient.

glands after the administration of 10 microcuries of I^{131}. The assumptions as to the per cent of the administered dose of I^{131} taken up by the thyroid, as well as the biologic half-life, are shown in the table. It is interesting to note that the highest dosage in e.r. for a hyperthyroid patient with a calculated uptake of 60 per cent of the 10-microcurie dose is only about one half the dosage in roentgens delivered to the skin during a routine GI series.

Table 2 shows a representative series of 4 patients in which consecutive uptake studies were done using the wide-angle scintillation counter, the directional scintillation counter and a shielded end-window Geiger-Müller tube. As nearly as possible, in each instance the detecting equipment was placed at such a distance from the thyroid that the solid angle which was covered encompassed the whole gland. The distances shown in the table are measured from the estimated center of the thyroid or the open glass bottle containing the dose to be administered, to the geometric center of either the Geiger-Müller tube or the calcium tungstate crystal. Two of these patients (D.J.H. and N.R.W.) were hypothyroid, one (E.P.N.) was euthyroid, and the fourth (E.J.W.) was hyperthyroid. All 4 patients were given tracer doses of carrier-free I^{131} varying, as shown in Table 2, from 10 to 20 microcuries; one week later, they were given tracer doses of from 100 to 318 microcuries. Two different amounts of tracer radioiodine were administered in order to demonstrate the validity of using small doses of the order of 10 microcuries in order to study either the rate

of uptake or the total uptake of inorganic I^{131} by the thyroid gland. Data for the rate of uptake of 1 to 10-microcurie doses of I^{131} by the thyroid will be presented in a subsequent report.

As indicated in the fourth column in Table 2, there is good agreement between the per cent of the administered dose taken up by the thyroid as determined by the wide-angle scintillation counter, whether a small dose of 10 to 20 microcuries or a larger dose of 100 to 318 microcuries be used.

TABLE 2. COMPARISON OF PER CENT UPTAKE OF I^{131}

1. Tracer doses of 10–20 *vs.* 100–318 microcuries.
2. Wide-angle scintillation counter *vs.* directional scintillation counter *vs.* end-window Geiger-Müller tube.

Patient	Hours after admin. of dose	μc. I^{131} admin.	Per cent uptake		
			Wide-angle scintillation counter[a]	End-window Geiger-Müller tube[b]	Directional scintillation counter[c]
D.J.H.	4	20	10.5	*	*
	6	318	10.7	13.3	12.4
	22	20	21.0	*	*
	28	318	23.8	23.2	19.4
N.R.W.	5	10	10.3	*	*
	6	200	13.5	17.5	14.6
	22	10	8.3	*	*
	25	200	13.0	12.7	11.0
E.P.N.	5	13.6	15.8	*	*
	6	182	12.1	12.6	12.3
	15	182	22.6	25.1	18.9
	27	13.6	27.9	*	*
E.J.W.	6½	13.6	53.1	*	*
	7	100	69.8	57.9	69.0
	21	13.6	61.4	*	*
	27	100	65.0	57.3	68.0
	44	13.6	60.0	*	*
	47	100	61.5	48.9	60.6

* Counts per second over the thyroid were less than 1×background.

[a] Wide-angle scintillation counter set at either 11 or 16.4 cm. from thyroid and admin. dose.

[b] End-window Geiger-Müller tube set at either 10 or 20 cm. from thyroid and admin. dose.

[c] Directional scintillation counter set at either 20 or 30 cm. from thyroid and admin. dose.

Any deviations in the percentage uptakes for the two doses are within the errors that may be expected from replicate determinations of this type made after a one-week interval. The comparison between small and large tracer doses could not be made with either the end-window Geiger-Müller tube or the directional scintillation counter, since they were not sensitive enough to detect the radiation from the I^{131} when small doses were used.

If a comparison is made between the per cent of the dose taken up by the thyroid, using large tracer doses, as indicated by the wide-angle scintillation counter, the end-window Geiger-Müller tube and the directional scintillation counter (as shown in Columns 4, 5 and 6, Table 2), it is apparent that reasonable agreement is obtained. The greatest differences in the per cent uptake figures between the three tubes occurred on patient E.J.W. In this case the Geiger-Müller tube indicated a somewhat lower percentage uptake than either of the scintillation counters. It was found later on making an "isocount" silhouette of the gland that one lobe of the thyroid was approximately three times the size of a normal lobe. This being the case, the Geiger-Müller tube set at 10 cm. from this lobe, as was done in this case, would not cover the entire radioactive area and therefore the calculated per cent uptake would be less than the true value.

As shown in Table 2, patient N.R.W. was given a small tracer dose of 10 microcuries of I^{131}. In five hours his thyroid had taken up 10.3 per cent, or slightly more than 1 microcurie of radioiodine. The net counts per second recorded with the wide-angle scintillation counter were 20.4. This count is 7 times the background recorded for this counter; therefore, even though this hypothyroid patient took up only 10.3 per cent of the administered dose of 10 microcuries, a dose of only 5 microcuries would have been adequate to determine accurately the per cent uptake, since even under these conditions, the net count would be 3 to 4 times background. In euthyroid and hyperthyroid states, in which a greater percentage uptake is to be expected, tracer doses of as little as 1 microcurie should be adequate. Even when using only a 1-microcurie tracer dose, a hypothyroid patient would be distinguishable from those with other thyroid states, due to the fact that little or no uptake would be detectable with the wide-angle scintillation counter.

DISCUSSION

New tools, the directional and the wide-angle scintillation counter, have been added to the armamentarium of the physician and the scientist interested in various clinical diagnostic and therapeutic applications of radioisotopes. The increased sensitivity of these instruments as detectors of the gamma radiation from radioiodine as compared to the conventional Geiger-Müller tube has made possible an extension of the usefulness of radiotracers, particularly in clinical studies.

In the employment of radioiodine as a therapeutic agent, one must know the actual dose delivered within the mass of thyroid tissue in order to correlate this with the therapeutic response. It is not enough to know only the dose administered. The direct measurement of the radiation delivered to an organ or tissue is impractical at the present time; however, if the physical properties of the radioisotope such as the half-life and radiation energy and the metabolic status of the tissue are known, it is possible to make a satisfactory indirect estimate of the radiation delivered to the tissue in terms of equivalent roentgens. In order to determine the e.r. delivered to thyroid tissue, it is necessary to know the concentration of radioiodine in microcuries per gram of tissue and its biologic half-life within the tissue. In order to determine the microcuries of iodine per gram of thyroid, the precise weight of the thyroid must be known as well as the total amount of radioactive iodine present in the gland. The determination of the percentage of a known dose of administered radioiodine that is present in the thyroid gland and the biologic half-life are fairly well standardized procedures and can be determined with a reasonable degree of accuracy by the various technics now employed. Of the factors involved in the calculation of dosage, the determination of the size and weight of the gland is by far the most difficult and at the present time constitutes one of the largest single errors in dosage calculation and, consequently, the evaluation of therapy in the treatment of hyperthyroidism and carcinoma of the thyroid.

The directional scintillation counter affords a degree of resolution such that relatively precise frontal and lateral silhouettes of the lobes of the thyroid gland may be outlined. These silhouettes represent the area covered by the thyroid, and thus offer a means of calculating thyroid volume and weight. Thus, for the first time it appears that it will be possible to eliminate the errors inherent in the present methods of estimating the weight of the thyroid gland.

When used as a diagnostic instrument, the directional scintillation counter by virtue of its increased sensitivity and hence its increased resolving power permits a precise in vivo determination of the relative distribution of radioiodine within the thyroid gland and thus will be of value in identifying hyperfunctioning nodules, with or without thyrotoxicosis, or in the identification of nonfunctioning nodules in a diffuse hyperfunctioning gland.

Another important diagnostic application of the directional scintillation counter, which has proved to be of considerable value and interest to the surgeon, has been the determination of the extent of a previous subtotal thyroidectomy or the completeness of a total thyroidectomy by outlining the residual thyroid tissue in cases of thyroid carcinoma in which no oper-

ative history is available. In a number of postoperative cases, it has been possible to outline paratracheal regions of radioactivity which probably represent residual normal thyroid tissue in the region where the recurrent laryngeal nerve approximates the thyroid gland.

The directional scintillation counter can also be used as an instrument for determining the uptake of radioiodine by the thyroid. For this purpose the conventional tracer doses of 50 to 250 microcuries of radioactive I^{131} are required. Because of the restricted solid angle covered by this counter, it is necessary to place it some 20 to 50 centimeters from the gland in order to determine the uptake of radioiodine. Thus, larger doses than 10 microcuries are necessary with this instrument.

It is well recognized that the basal metabolic rate as performed under average hospital conditions has many limitations, as has the more reliable protein-bound iodine determination (8, 9). As a possible substitute for these tests, the value of radioiodine uptake and radioiodine excretion studies as accurate diagnostic tests for various thyroid disorders has been demonstrated by numerous investigators (2, 11, 12, 13). The principal and most serious obstacle to the general use of radioiodine for diagnosis has been the possibility of producing radiation damage to thyroid tissue and to various organs of the body such as the kidney, gonads, pituitary and parathyroid glands. To date, medical science has been limited in the minimum amount of radioiodine that can be administered as a tracer dose and still result in reliable thyroid uptake studies. This amount, according to the current literature, ranges from 50 microcuries to 250 microcuries. As mentioned earlier in this text, this limitation in the minimum dosage that can be administered is due to the relative insensitiveness of the conventional Geiger-Müller tube to gamma rays. The wide-angle scintillation counter provides an extremely sensitive detector for the gamma radiation emitted by eight-day radioiodine. Its use makes possible the in vivo study of thyroid physiology, using tracer doses of the order of 1 to 10 microcuries instead of the conventional doses of radioactive I^{131}. Ten microcuries of carrier-free radioactive I^{131} have been used in urinary excretion studies as a diagnostic test for thyroid dysfunction (11). Here, however, one is not concerned with the in vivo measurement of gamma radiation but with in vitro measurements of I^{131} in the urine.

The ionizing radiation which is delivered to the thyroid gland from tracer doses of from 1 to 10 microcuries of eight-day iodine is less than that from some of the accepted diagnostic x-ray laboratory procedures now in common use. Thus, if the wide-angle scintillation counter is employed, and if tracer doses of 1 to 10 microcuries are administered, it is felt that radioiodine can now be added to the numerous diagnostic tests available for thyroid dysfunction without fear of any greater danger to the patient

from radiation damage than that attending many x-ray procedures now in use.

The introduction of the wide-angle scintillation counter should make possible the use of radioiodine for diagnostic purposes in many institutions that do not have the facilities or personnel for the handling of large quantities of radioactive isotopes as required by the Atomic Energy Commission. In addition, since only limited amounts of tissue irradiation will result from the use of small tracer doses of 1 to 10 microcuries of I^{131}, it is possible that its use as a diagnostic tool in thyroid dysfunction may be expanded to cover patients in all age groups.

SUMMARY

1. Reliable thyroid-uptake studies using doses as small as from 1 to 10 microcuries of eight-day radioactive iodine are now possible in the human being, using a new type gamma detector, the wide-angle scintillation counter. Such doses expose patients to less radiation than that obtained from some of the more common diagnostic x-ray procedures.

2. Precise outlining of the thyroid gland or other areas of radioactivity is now possible, utilizing the directional scintillation counter. A simple technic for delineation of the gland is described.

3. A description of the two types of scintillation counters is given: a directional scintillation counter 27 times more sensitive, and a wide-angle scintillation counter 94 times more sensitive, than the conventional end-window Geiger-Müller tube.

4. The application of these two scintillation counters to other types of clinical radiotracer studies has been discussed.

Acknowledgments

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IRRADIATION OF THE PITUITARY IN THE TREATMENT OF MALIGNANT EXOPHTHALMOS

WILLIAM H. BEIERWALTES, M.D.

From the Department of Internal Medicine, University Hospital, University of Michigan Medical School, Ann Arbor, Michigan

PROGRESSIVE protrusion of the eyes may occur in the presence of severe or mild thyrotoxicosis, after successful treatment of this toxic state, or in patients exhibiting no evidence of thyroid disease. This progressive exophthalmos may be spontaneously or artificially interrupted before any other eye signs or symptoms develop. If further progression of the exophthalmos occurs, however, certain accessory signs and symptoms may appear which characterize the clinical picture of "malignant exophthalmos." These features have been described by Mulvaney (1) and others (2–4). The initial symptoms are usually orbital, retro-orbital, or frontal pain; burning; lacrimation; photobia; and, less commonly, diplopia. The eyes become obviously proptosed. The lids swell. Edema fluid appears under both bulbar and palpebral conjunctivae. These conjunctival sacs may protrude between the lids in transverse bands or hang down over the cheeks for a distance of several centimeters. The palpebral aperture may increase in size. When the patient loses his ability to close the eyes at night while asleep, the conjunctiva tends to dry. Exposure keratitis, corneal ulceration, panophthalmitis, surgical loss of the orbit, or, rarely, death from meningitis may then follow (3).

Present knowledge of the etiology of this alarming disease has been well summarized by Means (4): "The etiology of malignant exophthalmos is unknown. Presumably it is a manifestation different in degree only from the exophthalmos seen in the ordinary case of Graves' disease. . . . It is also impressive that many bits of evidence favor the view that there is hyperfunction of the anterior lobe in a human disease of which exophthalmos is a frequent manifestation. But whether the anterior pituitary agent involved is identical with that which exercises the tropic action on the thyroid parenchyma, or something else which comes down in the same fraction, has not yet been determined."

Treatment of malignant exophthalmos has consisted of local care of the eyes, lowering of the basal metabolic rate when elevated, the administration of desiccated thyroid in an attempt to depress the pituitary's output

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of thyrotropic hormone, and, if these measures fail, surgical decompression of the orbit.

McCullagh (5) suggested that irradiation of the pituitary might be a rational approach to the treatment of malignant exophthalmos because of "evidence suggesting the pituitary might be a source through its output of thyrotropic hormone of both Graves' disease and exophthalmos," the known effect of x-rays on basophil tumors of the pituitary in Cushing's disease, and the decrease in size of certain other pituitary tumors as evidenced by relief of optic nerve compression. Means (6) tried x-ray treatment of the pituitary in 1 case of malignant exophthalmos. "In that one, rapid and impressive improvement occurred, but it may not have been due to the treatment." Thompson and Thompson (7) used it in 38 cases of toxic goiter. The metabolism fell in 23. The authors did not state what the effects were on the condition of the eyes. Review of the literature has revealed no article written specifically on the use of irradiation of the pituitary for the treatment of malignant exophthalmos. Dobyns (8) has indicated, however, that as many as 37 patients so treated have been mentioned in articles not primarily concerned with this form of treatment. These articles contribute little to the present thesis because they are, for the most part, reports of isolated cases either not followed objectively with an exophthalmometer, or else followed for too short a time. The pretreatment periods offered inadequate controls for post-treatment observations in many instances. The results were generally disappointing, although an occasional excellent response has been noted (5–6).

In the present study, irradiation of the pituitaries of 10 patients with malignant exophthalmos and 1 with obstinate progressive exophthalmos was carried out because of the logic of the use of this form of therapy in such a serious condition, the apparent lack of toxic effects (5), and the disappointing results obtained with other forms of treatment short of surgical decompression. Since our results were heartening and the patients were followed closely with photographs, muscle biopsies, and exophthalmometer measurements for periods up to five years, it seems worthwhile to report our results.

MATERIAL AND METHODS

Ten patients had two or more of the objective characteristics of malignant exophthalmos described above. They form a selected group, in that danger of loss of vision was imminent, as evidenced by the progress of objective manifestations of malignant exophthalmos while under therapy with desiccated thyroid. Six patients were white, 3 of these being male. Of 4 colored patients, 1 was male. The age range was from 32 to 71 years. One hundred and three representative exophthalmometer measurements

were charted out of a total of 200 performed on these patients. Each reading was made in the afternoon by a member of the Ophthalmology Department,[1] using the same baseline in consecutive measurements on a given patient. These readings were repeated in most cases at intervals of one or two months. The period of such observation averaged twenty-three months ranging from six to forty-eight months. Local therapy not usually noted on our graphs were tarsorrhaphy, vaseline gauze pads applied over the eyes, and antibiotics. Nine of the 10 patients were seen by the author throughout the course of follow-up for evaluation of the eyes, thyroid function, and toxic effects of radiation. Sixty basal metabolic rate determinations were performed in the course of this study. X-ray therapy was given under the direction of Dr. Isadore Lampe, Department of Roentgenology, using two temporal fields and, in addition, an anterior nasal field in 2 patients. A representative technique used employed 200 K.V., 25 M.A., 50 T.S.D., filtration 0.5 mm. Cu plus 1 mm. Al, H.V.L. 1.0 mm. of Cu, r per minute in air approximately 40, 150 as measured in air to each field each day to a total of 700 r per field, with a field size of 8×7 cm.

RESULTS

Nine of the 10 patients were treated before radiation with 0.1 Gm. of desiccated thyroid, U.S.P., per day for an average control period of 10.7 months, ranging from 0.5 to 22 months. The average progression in exophthalmos during this period was +2.7 mm. O.D. and +1.1 mm. O.S. The average duration of follow-up with exophthalmometer measurements after radiation therapy was 13 months, ranging from 5 to 31 months. The average interval between radiation therapy and the beginning of recession in patients later enjoying a significant recession in exophthalmos, *i.e.*, 2 mm. or more, was three months, ranging from 0.7 to 5.0 months. The average interval between radiation therapy and maximum recorded recession of the eyes was 11.8 months, ranging from 3.5 to 24 months. After radiation therapy, 7 patients had significant recession in exophthalmos in either right (six) or left (four) eyes, or both. The average in the 6 patients with response O.D., was −5.7 mm. and in the 4 with response O.S., −5.3 mm., ranging from −2 to −13 mm. O.D., and −2.7 to −12.0 mm. O.S. The eyes of the 3 patients showing no significant recession in exophthalmos in either eye registered an average increase in protrusion of +0.33 mm. O.D. and +0.66 mm. O.S. (not significant). Only 1 of these patients showed a significant increase in exophthalmos during the post-irradiation

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[1] Dr. F. B. Fralick, Chairman of this Department, contributed generously in referring these patients to the author for observation and in securing many photographs and muscle biopsies.

period, amounting to +2 mm. O.U. It should be noted that, in the group enjoying significant recession of exophthalmos, 1 patient showed a recurrence of the eye protrusion after maximum eye recession had taken place.

Other factors conceivably influencing the eye response to irradiation of the pituitary were recorded. The average weight gain after irradiation was 13 pounds in the group with significant eye recession, and 8 pounds in the unresponsive group. The decrease in basal metabolic rate during the post-irradiation period was −2.1 per cent in the responsive group, and −21 per cent in the unresponsive group. This latter figure is based on only 2 of the 3 patients.

The following case abstracts, charts, and photographs present results of treatment in 6 representative patients.

CASE REPORTS

Case 1. Malignant exophthalmos with no apparent thyroid disease

C. P., 569380, a 33-year-old colored female, was first seen at the University Hospital on May 15, 1945, with the complaint of "bulging eyes." In March, 1945, the patient had a "sore throat" which subsided spontaneously in a few days. One week later her left eye "began to pain." A few days later the right began to pain. The conjunctivae and sclerae of both eyes became very red. A private physician "taped her eyes" and gave her penicillin by injection, and sulfa drugs and fluids orally. Symptoms and signs progressed. The patient claimed she lost her vision completely three days before admission. She had experienced no symptoms of hyperthyroidism. The pertinent physical findings were a pulse rate of 112 and a temperature of 99.8°. No signs of thyrotoxicosis

FIG. 1. Case 1. Histologic section of extraocular muscle biopsy specimen obtained June 6, 1945. "This material consists of adipose tissue, voluntary muscle and fascia. They all show a diffuse chronic inflammatory reaction with some lymphocytic infiltration. No evidence of neoplasm." (Dr. C. V. Weller).

or hypothyroidism were evident. No goiter was present on inspection or palpation. There was marked swelling of the upper lids, more pronounced on the left. The lower palpebral conjunctivae were everted and extremely chemotic. There was an extreme bilateral proptosis, and intense injection and some chemosis of the bulbar conjunctivae. There was marked restriction of ocular movement in both eyes.

The basal metabolic rate on admission was −12 per cent. A complete blood count showed no abnormality. X-ray examination showed a normal skull and paranasal sinuses and there was no sign of a substernal thyroid. There was a small nodule present in the upper eyelid on the right. A biopsy specimen from this nodule was examined microscopically by Dr. C. V. Weller, Chairman of the Department of Pathology, on June 6, 1945. He reported as follows: "This material consists of adipose tissue, voluntary muscle

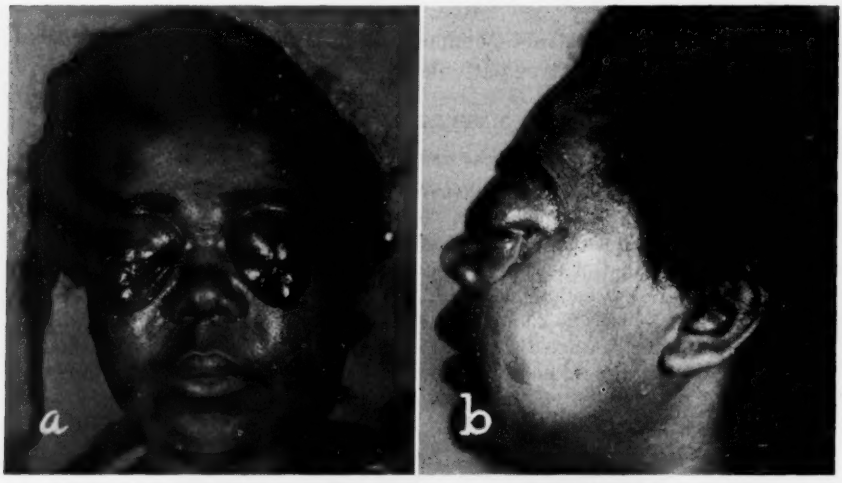

FIG. 2 (*a* and *b*). Case 1. Photographs of patient's eyes on July 11, 1945, before irradiation of the pituitary.

and fascia. They all show a diffuse chronic inflammatory reaction with some lymphocytic infiltration. No evidence of neoplasm" (Fig. 1).

The patient was treated with desiccated thyroid, U.S.P., and strong iodine solution, U.S.P. On July 11, 1945, photographs were taken of her eyes (Fig. 2, a and b). She was transferred to the Department of Neurosurgery on July 14, and on July 18 a bilateral frontal craniotomy was performed by Dr. Robert C. Bassett, and the superior and lateral walls of both orbital cavities were removed. Because the exophthalmometer measurements did not decrease in the first five weeks postoperatively, the pituitary was irradiated on August 16, 600 r to a right, left, and one anterior field.

The patient was discharged August 26, 1945, not taking any medication and advised to return in three weeks. She did not, however, return until July 28, 1947. At this time, the extraocular movements were full and normal. There was increased resistance in the orbits. The point of basal convergence was 110. The lids were normal. There was a 5-mm. fold of hypertrophied conjunctiva just above the lower lid on the right, and a 2-mm. fold under the left lower lid. The conjunctiva below the lid was normal (Fig. 3). A graphic

FIG. 3. Case 1. Photograph of patient's eyes July 28, 1947, two years after irradiation of the pituitary, and without medication.

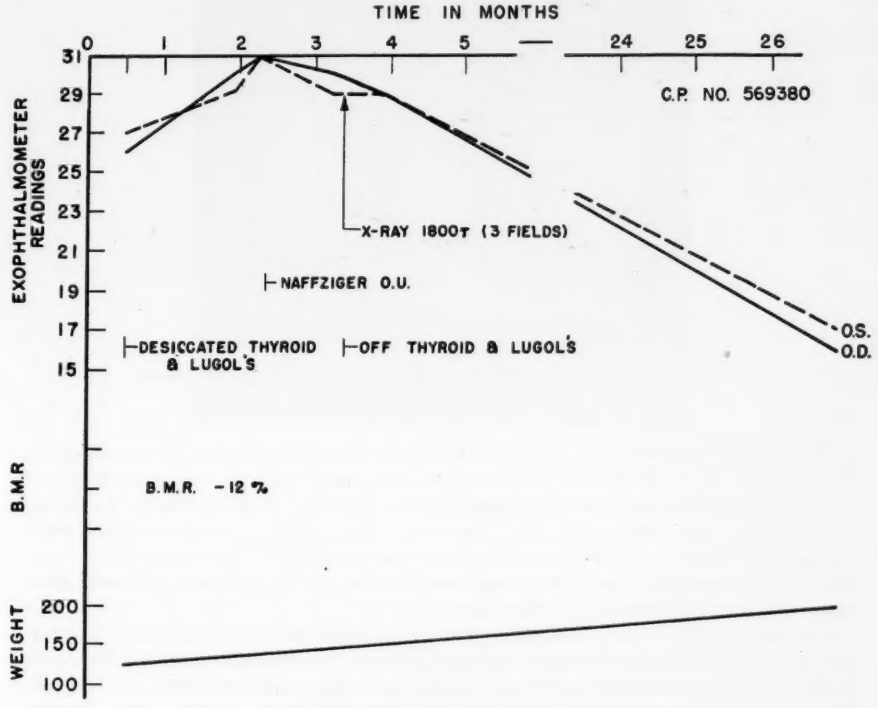

FIG. 4. Case 1. Graphic summary of exophthalmometer measurements, treatment and weight in Case 1.

representation of her exophthalmometer measurements, treatment, and weight are given in Figure 4.

Summary: A 33-year-old colored woman experienced the development of severe malignant exophthalmos over a period of two months. There were no symptoms or signs of thyroid disease, and the B.M.R. was −12 per cent. The eyes became worse during a short trial of desiccated thyroid. The patient showed no improvement during the first five weeks after a Naffziger decompression. X-ray treatment of the pituitary was followed by a 12-mm. decrease in the exophthalmos in both eyes and almost complete disappearance of the accessory signs of malignant exophthalmos.

Case 2. Malignant exophthalmos and slight elevation of the B.M.R., with no signs or symptoms of thyroid disease

M.S., 529891, was a 53-year-old white male when first seen at this hospital on July 22, 1943, with the complaint of "bulging of the eyes." In 1937 he had first experienced

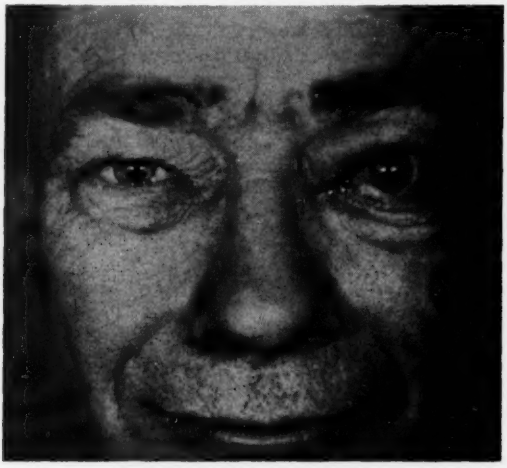

FIG. 5. Case 2. Photograph of eyes on February 21, 1945, before irradiation of the pituitary.

redness of the right eye, with some pain but no swelling or discharge. These symptoms lasted about one week. He was then asymptomatic until January 1941, when he noted painless prominence and redness of the right eye and lids, these symptoms becoming progressively more pronounced until December 1943, and then remaining stationary. He had experienced no diplopia except on extreme lateral gaze. The patient related that he had received one course of x-ray treatment to the right eye in April 1941, with some apparent, though temporary, improvement.

On physical examination, his blood pressure was found to be 145/95. The thyroid was not palpable. The exophthalmometer readings were 16 mm. O.D. and 13.5 mm. O.S. Extraocular movements were normal. There was no hyperemia or edema of the orbit. The palpebral fissures were 9 mm. O.D. and 8 mm. O.S. There was no palpable tumor in the orbit, and no bruit or thrill over the thyroid. The ocular fundi were normal. The globes were compressible. The white blood cell count was 6,700. The red blood cell

count was 4.4 million. The differential white blood cell count was normal. On December 27, 1943, there was edema of both the upper and lower lids bilaterally, with chemosis of the conjunctiva on the right. There was no limitation of motion or diplopia. Palpebral fissures were 10 mm. O.D. and 8 mm. O.S. No palpable mass was felt. Exophthalmometer readings were 20 mm. O.D. and 15 mm. O.S. There was still edema of the lids and conjunctiva. On February 21, 1945, the patient was taking 1 grain of desiccated thyroid daily and strong iodine solution, U.S.P. The right conjunctiva had become red and

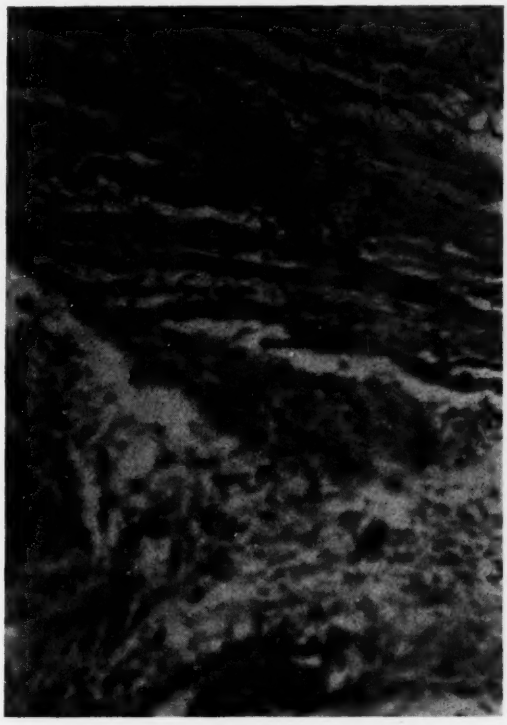

FIG. 6. Case 2. Histologic section of biopsy specimen from the right external rectus and inferior oblique muscles of the eye. Edema and round-cell infiltration of the muscle bundles. (Courtesy of S. C. Howard, M.D., St. Joseph's Mercy Hospital, Ann Arbor, Michigan.)

edematous three to four months before this visit, and the proptosis had become more severe. There was limitation of motion on the right. There was hyperemia and chemosis of the conjunctiva and edema of the lids on the right, and slight edema of the lids on the left. Exophthalmometer measurements were 24 mm. O.D. and 14 mm. O.S. Photographs of the eyes were taken (Fig. 5). On March 8, 1945, a biopsy specimen was taken from the right external rectus and the inferior oblique muscles. Pathologic examination showed edema and round-cell infiltration of the muscle bundles (Fig. 6). On April 20 the exophthalmometer readings were 29 mm. O.D. and 17 mm. O.S. The B.M.R.,

during the administration of 2 grains of desiccated thyroid per day, was +14 per cent. The patient was given stilbestrol, 1 mg. daily. On April 1, 1946, the eye measurements were 28 mm. O.D. and 16. mm. O.S. X-ray therapy was given as in Case 1, 400 r to two temporal and one anterior nasal field. On April 15 and July 29, 1946, the exophthalmometer readings were 20.5 mm. O.D. and 15 mm. O.S. On July 29 the course of x-ray therapy was repeated. On October 28, 1946, the readings were 17 mm. O.D. and 14 mm. O.S. Figure 7 gives a summary of the exophthalmometer measurements, basal metabolic rates, and treatment during three and a quarter years of observation.

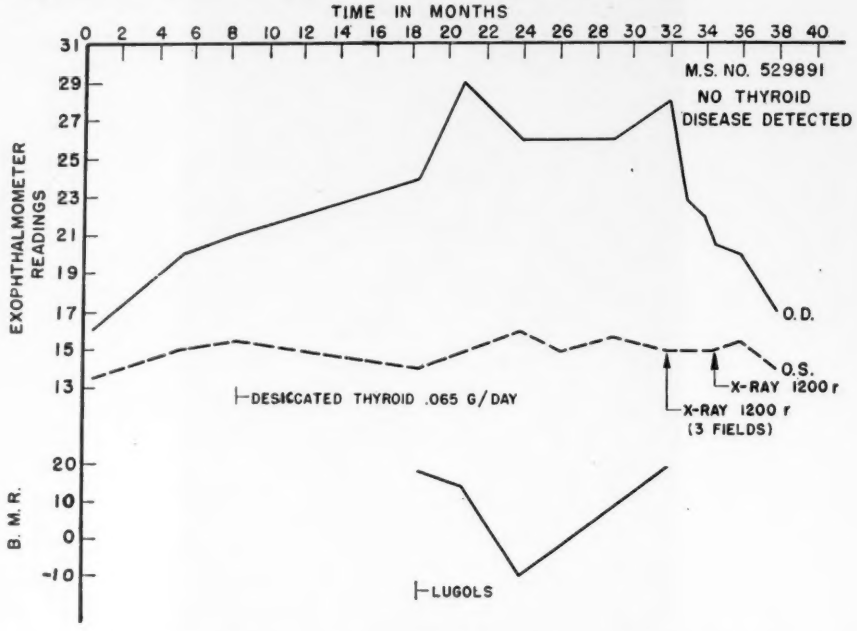
TIME IN MONTHS
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
M.S. NO. 529891
NO THYROID
DISEASE DETECTED
EXOPHTHALMOMETER READINGS
31 29 27 25 23 21 19 17 15 13
O.D.
O.S.
X-RAY 1200 r
X-RAY 1200 r
(3 FIELDS)
DESICCATED THYROID .065 G/DAY
B. M. R.
20 10 0 -10
LUGOLS

FIG. 7. Case 2. Graphic summary of exophthalmometer measurements, B.M.R., and treatment during three and a quarter years of observation.

Summary: This 53-year-old white male had had eye difficulty, mainly unilateral, for six years. He was treated with desiccated thyroid and strong iodine solution, U.S.P., for almost three more years before it seemed necessary to resort to x-ray therapy. During the ensuing six months, his eyes receded 11 mm. O.D. and 2 mm. O.S.

Case 3. Malignant exophthalmos and moderately severe thyrotoxicosis, with coincident olivo-ponto-cerebellar atrophy

B.S., 603289, a 34-year-old colored male, was seen at University Hospital on November 7, 1946, with the complaint of "eyes popping out." Six months before admission, he had experienced the rapid onset of classic symptoms of thyrotoxicosis. Two months before admission, he had blurring of vision and diplopia, and he and his friends had noted increasing prominence of his eyes. One month before admission, his physician had started treatment with strong iodine solution, U.S.P., and sedation.

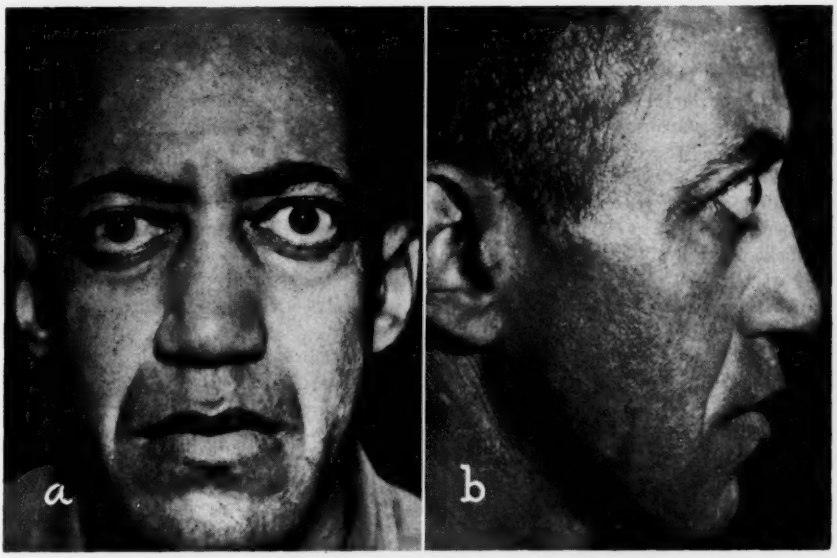

FIG. 8 (*a* and *b*). Case 3. Photograph of eyes two years after x-ray treatment of the pituitary, for malignant exophthalmos.

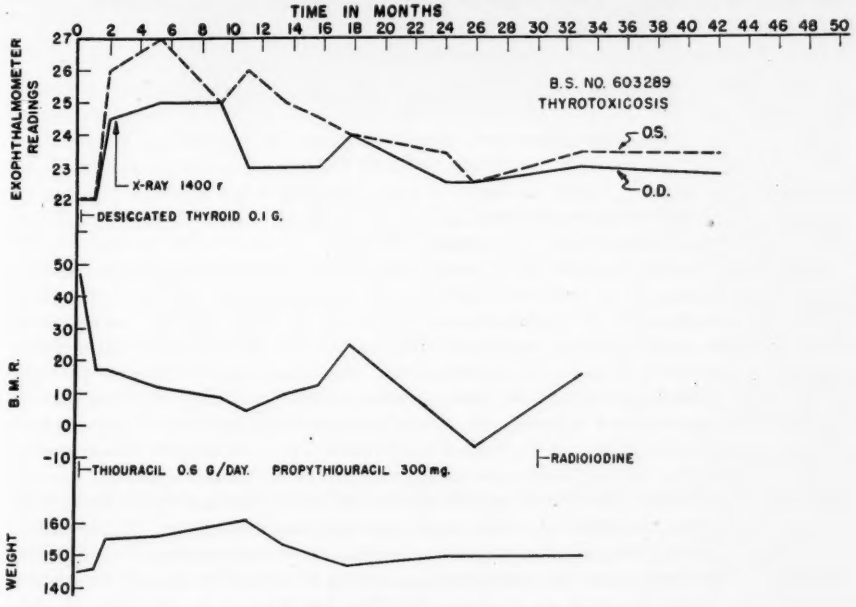
TIME IN MONTHS
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50
EXOPHTHALMOMETER READINGS
27 26 25 24 23 22
B.S. NO. 603289
THYROTOXICOSIS
O.S.
O.D.
X-RAY 1400 r
DESICCATED THYROID 0.1 G.
B. M. R.
50 40 30 20 10 0 -10
THIOURACIL 0.6 G/DAY. PROPYTHIOURACIL 300 mg.
RADIOIODINE
WEIGHT
160 150 140

FIG. 9. Graphic summary of course in Case 3.

On physical examination, the blood pressure was 150/85, pulse 120, and respirations 24. He was overactive. The skin was hot and moist. There was apparent marked bilateral proptosis. Exophthalmometer measurements were 22 in each eye. Extraocular movements and ocular fundi were normal. The lids were slightly edematous, more marked on the left. The palpebral fissures closed completely. There was a fine tremor of the protruded tongue. There was no gross thyroid enlargement and no bruit or thrill was heard or felt. There was a fine tremor of the extended fingers. Dr. Charles M. Wilson, neurologist, noted that the patient's brother had been a patient at this hospital, and that his case had been diagnosed as "a degenerative disease of the cerebellar connections, olivo-ponto-cerebellar atrophy." Dr. Wilson found changes on neurologic examination in our patient that were compatible with the same diagnosis. The results of a complete blood count and urinalysis were normal. The basal metabolic rate was +47 per cent, basal pulse 98, and plasma cholesterol 151 mg. per cent.

The patient was treated with 150 mg. of propylthiouracil and 0.1 Gm. of desiccated thyroid, U.S.P. The B.M.R. fell below +20 per cent in five weeks and remained at a level of from −6 per cent to +18 per cent for the next two and a half years. Because of an increase in exophthalmos of 3 mm. O.D. and 5 mm. O.S. and the simultaneous appearance of right corneal ulceration, the pituitary was irradiated during the period from January 28 to February 5, 1947, 800 r to each of two lateral pituitary fields. During the next two years, the exophthalmos decreased 2.5 mm. O.D. and 4.5 mm. O.S. Figure 8 (a and b) shows front and lateral views of his eyes at the end of this period. Figure 9 gives a graphic representation of his entire course.

Summary: This 34-year-old colored male had malignant exophthalmos developing eight months before x-ray treatment of the pituitary. Regression of exophthalmos to the extent of 2.5 mm. O.D. and 4 mm. O.S. occurred over the ensuing two years.

Case 4. Malignant exophthalmos and severe thyrotoxicosis

G.K., 568847, was a 58-year-old white male when first seen at University Hospital on May 7, 1945, with the complaint of bulging of the eyes. He was well until February 1944, when he had a severe eight-hour bout of diarrhea. He rapidly lost weight after this from 165 to 135 pounds. In February 1945, he began to have classic symptoms of thyrotoxicosis. March 1, 1945, he began to notice bulging of his eyes and blurring of vision and diplopia when his eyes were in certain positions. He noted that liquids occasionally returned when he tried to swallow them.

On physical examination the blood pressure was 124/50, and auricular fibrillation was present. His vision was found to be 3/60 O.D. He counted fingers at 1 ft. O.S. uncorrected; with correction, he counted fingers at 5 ft. O.D. Both eyes showed exposure necrosis of the cornea and subacute iridocyclitis (Fig. 10). The patient's initial basal metabolic rate was +73 per cent. Thiouracil was started in a dose of 0.6 Gm. per day. At the time of discharge on June 16, 1945, his basal metabolic rate was +30 per cent. A three-band tarsorrhaphy was performed on each eye following admission. This procedure was successful on the right, but the medial band failed to hold on the left. There was no corneal staining on the right and minimal superficial staining on the left at the time of discharge. The cornea of each eye was well covered when the eye was closed. From time to time throughout the period of follow-up, the tarsorraphies broke down. On September 13, it was noted that the limitation of motion had decreased considerably on both sides. Because of the development of agranulocytosis during thiouracil therapy, the patient's thyroid was treated by x-ray on February 26, 1946. On May 23, it was noted by slit-lamp examination that lens sclerosis was progressing in the left eye. On July 24, 1946,

the patient began to notice blurring, and pannus veil was found to be encroaching on the pupillary area of both eyes, although more marked on the left. Moreover, the patient could no longer close his eyes completely. On January 23, 1947, it was noted that there were some posterior synechiae on the right, with no evident active iritis. During 1948, there was a progressive increase in the amount of pannus formation. On August 5, a lateral band tarsorrhaphy was performed. Because of the marked staining in the region of the pannus and the steady progression of signs, the patient's pituitary was irradiated with a total of 300 r to each of two temporal ports, on December 7, 1948. During the ensuing fifteen months, the patient enjoyed a progressive decrease in exophthalmos of

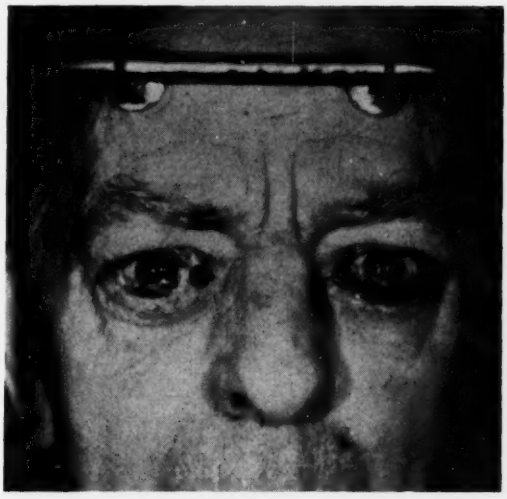

FIG. 10. Case 4. Photograph of eyes showing exposure necrosis of the cornea in both eyes.

3 mm. O.D. and 2 mm. O.S. The "frozen orbits" and extensive pannus formation in both eyes persisted unchanged. Figure 11 presents graphically his five-year course.

Summary: This 58-year-old male had severe thyrotoxicosis, with a B.M.R. of +73 per cent. One year after the onset of thyrotoxicosis, he noted the onset of exophthalmos and extraocular muscle paresis. Two months after these first eye symptoms, he was found to have exposure necrosis of the cornea and subacute iridocyclitis in both eyes. The thyrotoxicosis was resistant to proper management over a period of five years. During this time, x-ray treatment of the pituitary was followed by a significant decrease in exophthalmos, but the patient still retains extensive pannus and "frozen orbits" after numerous tarsorrhaphies.

Case 5. Moderately severe recurrent thyrotoxicosis with malignant exophthalmos after thyroidectomy

S.G., 648187, was a 53-year-old white woman when first seen on October 18, 1948, with the complaints of high blood pressure, goiter, and protrusion of the eyes. In October 1947, the patient noted tachycardia easily aggravated by the least exertion. Within a few weeks she noticed anterior neck fullness and choking sensations. There were also

other symptoms of thyrotoxicosis. The basal metabolic rate was +10 per cent. Symptoms progressed, and the patient lost 20 pounds in weight. She took strong iodine solution, U.S.P., for two weeks in preparation for a thyroidectomy, which was performed on December 16, 1947. During the two-week postoperative convalescence all symptoms of thyrotoxicosis disappeared but progressive puffiness developed above and below the eyes, with failure of vision. In the four to six weeks prior to admission, there was a return of all the symptoms noted before thyroidectomy, and for the first time she noted that her eyes were protruding. The basal metabolic rate on September 4, 1948, was +37, and on September 18 was +36. The patient had noted "black out" of the right visual field.

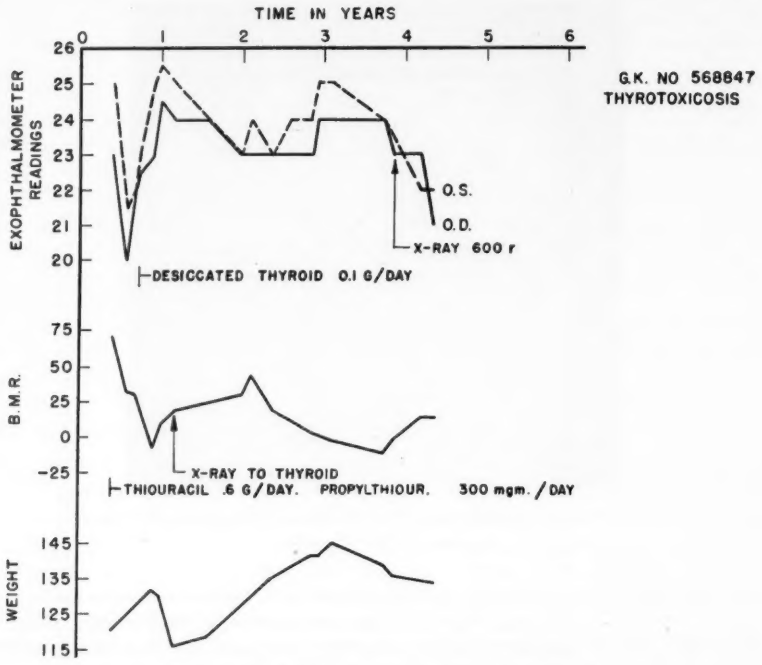

FIG. 11. Graphic summary of course in Case 4.

On physical examination, the blood pressure was 200/100 and the pulse 90. There was moderate limitation of motion of the eyes in all fields of gaze. The superior recti were the most seriously involved. The point of basal convergence was 110. By palpation, tension felt normal in both eyes. There was injection and chemosis of the conjunctivae on both sides. The eyes could be closed completely. The tongue protruded with a fine tremor. The thyroid was firm, slightly irregular, and enlarged (1 plus), with no definite nodules palpated. On admission, the patient was found to have a B.M.R. of +34 per cent. She was given propylthiouracil in a dose of 100 mg. three times daily, sedation with chloral hydrate, desiccated thyroid, 0.064 Gm. per day, and strong iodine solution, U.S.P., 4 drops per day. Her B.M.R. had fallen to +19 per cent at discharge.

On April 11, 1949, the patient received x-ray treatment of the pituitary in a dose of

FIG. 12. Case 5. Normal eyes, March 27, 1950, one year after irradiation of the pituitary.

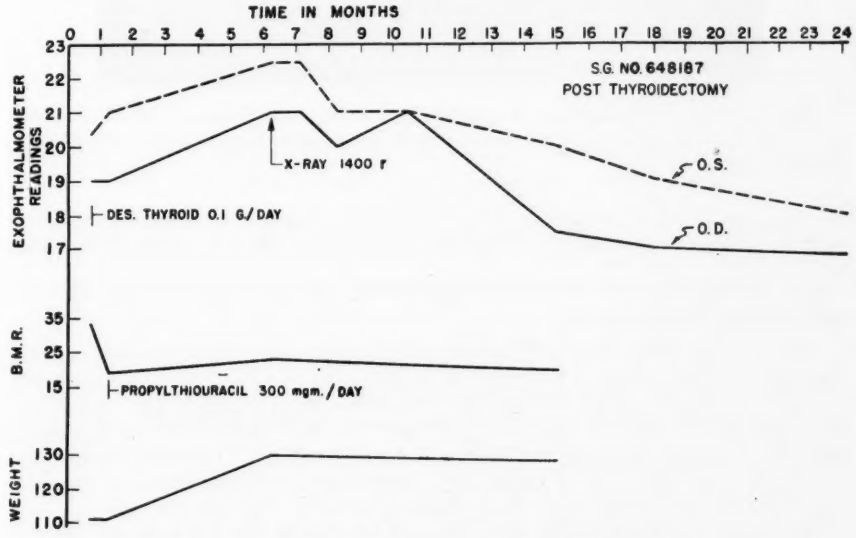

FIG. 13. Case 5. Graphic summary of course of Case 5.

700 r to each of two temporal fields, and continued on the same regimen. On May 15, she had a band of horizontal superficial punctate keratitis across the lower third of the cornea on the right. There was no flare and there were no cells. The keratitis was treated by boric acid ointment in both eyes three times daily and by June 13, 1949, it had disappeared.

The patient returned on March 27, 1950, with relatively normal exophthalmometer measurements. She was asymptomatic. She had only minimal residual swelling of the lids. Figure 12 is a photograph of her eyes at present. Figure 13 shows her course graphically.

Summary: This 53-year-old woman had malignant exophthalmos for ten months, beginning immediately after a thyroidectomy for exophthalmic goiter. Her eyes became worse during an additional six months' period of conservative treatment with desiccated

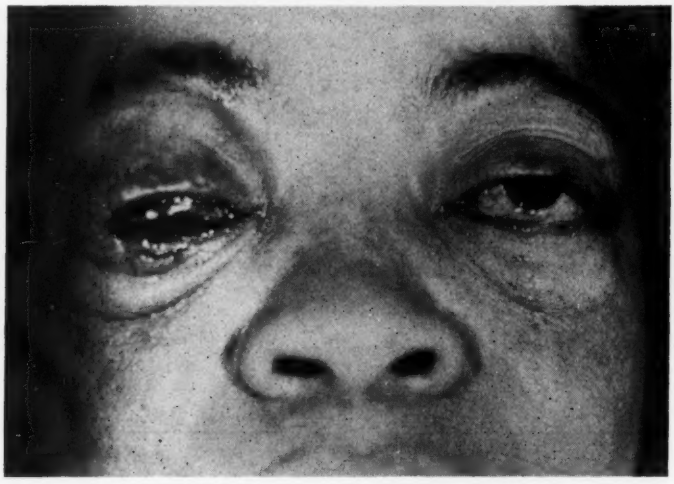

FIG. 14. Case 6. Photograph of eyes on January 6, 1949, before irradiation of the pituitary, showing bilateral ptosis, more marked on the right. Pannus and scar formation are seen on the right.

thyroid. Irradiation of the pituitary was followsd by progressive recession of the eyes to well within normal limits. At present there is no detectable abnormality of the eyes.

Case 6. Malignant exophthalmos (post-thyroidectomy) with no response to x-ray therapy, and complicated by glaucoma.

S.H., 652654, was a 45-year-old colored woman seen in this hospital January 6, 1949, with the complaint of pain in the right eye. In 1947 she had a classic onset of exophthalmic goiter, and in May 1948, thyroidectomy was performed. The patient had "two glands as big as your fist" removed. Just prior to the operation, her eyes protruded much farther, especially the right. She noted that the eyeball was "fiery red." The eyes became even worse after thyroidectomy. A lateral band tarsorrhaphy was performed on the right eye. She had been asymptomatic since operation, except in regard to her eyes.

On physical examination the blood pressure was 138/92 and the pulse 80. She appeared to be somewhat slowed. Her skin was smooth and dry. There was obvious marked

ptosis of both eyes, more pronounced on the right (Fig. 14). Exophthalmometer measurements were 34 mm. O.D. and 26 mm. O.S. In spite of the lateral band tarsorrhaphy, the nasal bulbar conjunctiva was exposed, hyperemic, and weeping. The lower third of the cornea was exposed, and there was a vast pannus invading the lower cornea, with considerable scar formation. The bulbar conjunctiva on the left showed mild exposure, with hyperemia and mucopurulent discharge. There was some tendency for entropia, with the cilia rubbing against the globe. However, when the eye was closed, the globe was covered adequately. Extraocular movements were limited markedly in all fields, and there was no ability to converge. There was no gross staining of either cornea. There was some staining of the conjunctiva on the right. There appeared to be generalized

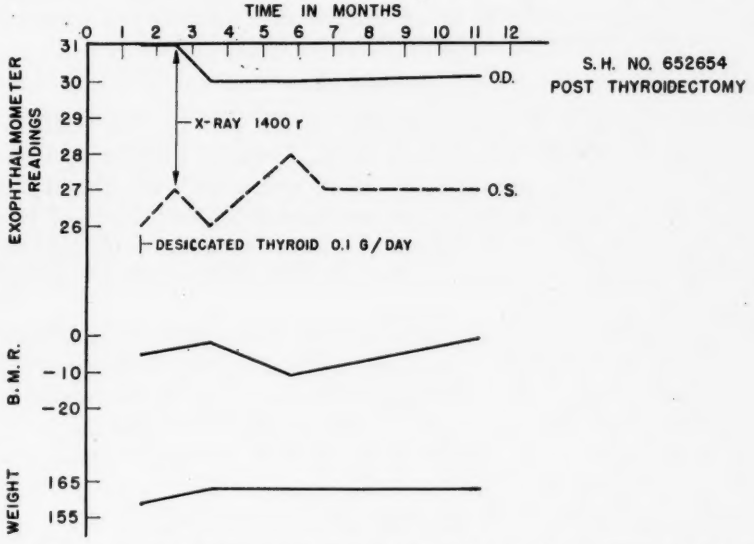

FIG. 15. Case 6. Graphic summary of course in Case 6, showing no response to irradiation of the pituitary during the time the patient was followed.

pallor of both discs. Slit-lamp examination on the right showed the bulbar conjunctiva to be markedly chemotic and hyperemic, with areas crusted over and bleeding. There was dense scarring of the inferior cornea, and deep pannus of vessels invaded the cornea in the scarred areas, though there was no staining of this area. Several lashes of both the upper and lower left lids were turned in and rubbed against the globe. The neck revealed two thyroidectomy scars, with a small draining sinus in each scar. There was much induration. There was no thyroid enlargement, however. There was scarring of both shins, which the patient stated was caused by burning at a fireside when a child. The basal metabolic rate was found to be −5 per cent, and 0.1 Gm. per day of desiccated thyroid, U.S.P., was started. On January 10, 1949, irradiation of the pituitary was begun. This was completed on January 17, with a total of 700 r to a left lateral pituitary field and 600 r to a similar field on the right. The patient noted progressive symptomatic improvement following the X-ray treatment. She received symptomatic therapy consisting of pilocarpine drops three times daily because of a diagnosis of simple glaucoma,

bilateral and chronic. Vaseline pads were used on the right eye at night. On February 16, all corneal staining had disappeared. When last seen on November 4, 1949, there was no significant change objectively. In Figure 15 the course of her disease is shown graphically. It should be noted that this patient had a biopsy specimen taken on January 12, 1949, from the left quadriceps muscle. On microscopic examination, Dr. J. A. French reported: "Increased voluntary muscle nuclei with a moderate perivascular inflammatory infiltration."

Summary: This 45-year-old colored female had exophthalmos that caused symptoms starting two weeks before thyroidectomy. Her eyes became worse the first few weeks after thyroidectomy. Complicating ptosis disguised the severity of her proptosis. Entropion and glaucoma complicated her course. Although only seven months had elapsed from the onset of her eye disease to time of irradiation of the pituitary, no objective decrease in exophthalmometer measurements has occurred to date.

DISCUSSION

The total number of patients treated in this series is too small to be statistically significant. There is no doubt, however, judging by history, physical examination, photographs before and after x-ray therapy, and repeated Hertel exophthalmometer measurements, that 7 out of 10 patients with malignant exophthalmos and 1 with progressive exophthalmos enjoyed a significant recession of their disease after radiation directed to the region of the pituitary.

The probability that this radiation was responsible for the ensuing change in the eyes is strongly suggested by the observation that 9 of the 10 patients with malignant exophthalmos became worse while treated with desiccated thyroid for an average control period of 10.7 months. It is unlikely, furthermore, that changes in the B.M.R. or weight influenced the eye response during the period of follow-up, since these factors showed no significant correlation. It should be mentioned in connection with Case 1, that Dr. Robert C. Bassett in our Department of Neurosurgery has recently observed a recession of the eyes in 1 patient, beginning one year after Naffziger decompression, without other forms of therapy in the interim.

It should be emphasized that the x-ray ports overlapped some extraocular soft tissue. The resultant radiation to extraocular tissues might conceivably account for some or all of the beneficial effects observed here, through decreasing the volume of extraorbital tissues. Although this interesting theoretical possibility warrants investigation, the fact remains that radiation applied to the areas described above was usually followed by improvement.

It is probable that the paucity of reports in the literature on the use of irradiation of the pituitary by roentgen-rays in the treatment of malignant exophthalmos is due to the relatively small number of patients with this disease which any one man has an opportunity to observe, the short follow-

up of patients so treated, and concern over the possible development of panhypopituitarism. The radiation therapist may see these patients for a re-evaluation one month after the treatment has been administered. He will probably see no change in this short interval, since our patients showed onset of recession of exophthalmos 3 months after radiation, and maximum recession at an average period of 11.8 months. He and the clinician are consequently apt to conclude that radiation therapy is of no benefit in this condition, and thus go on to a surgiccal decompression procedure prematurely.

The only unpleasant effects of radiation therapy as used in this study were mild headaches for three to seven days after radiation in a few patients and transitory epilation over the temporal areas in all patients; all enjoyed satisfactory regrowth of hair. The fact that these patients were followed for periods up to three years after radiation without the development of symptoms or signs of hypopituitarism strongly suggests that radiation used as previously described is not harmful to the patient. McCullagh (5) has performed urinary follicle-stimulating hormone assays, estrogen assays, and sperm counts on patients treated in this manner. His data affirm the lack of detrimental effect on other "target organs" of the pituitary.

Interesting complicating factors have been observed in association with malignant exophthalmos. One patient (Case 6) had entropion, thyrotoxic myopathy, and glaucoma. The clinical picture of thyrotoxic myopathy led us to perform a quadriceps muscle biopsy, the report of the findings being compatible with the diagnosis of thyrotoxic myopathy (8). One other patient, G.L., 585990, had glaucoma in addition to malignant exophthalmos. This complication has been described as not rarely associated with malignant exophthalmos (9). The association of olivo-ponto-cerebellar atrophy in Case 3 is thought to be fortuitous.

SUMMARY AND CONCLUSIONS

1. In patients with malignant exophthalmos, decrease in measurable protrusion of the eyes is rarely, if ever, brought about by lowering the basal metabolic rate when it is elevated, or by the administration of desiccated thyroid when it is not (10). Surgical decompression of the orbit is effective treatment in this condition, but is a relatively formidable procedure.

2. Roentgen-ray therapy directed to the pituitary was used in 10 patients with malignant exophthalmos and 1 patient with progressive exophthalmos. These patients were selected for treatment because their eye status became worse during an average control period of 10.7 months during which time they were treated with desiccated thyroid.

3. Seven of the 10 patients with malignant exophthalmos and 1 patient

with progressive exophthalmos enjoyed significant recession in exophthalmos, *i.e.*, 2 mm. or more, averaging −5.7 mm. O.D. and −5.3 mm. O.S.

4. Only 1 of the 3 nonresponsive patients showed a significant increase in exophthalmos.

5. The only other effects of radiation observed in follow-ups of as long as three years was transient epilation in all patients, and occasional headaches during the first few weeks after treatment.

6. Our responsive patients showed onset of post-irradiation recession at an average interval of three months and maximum recession at an average interval of twelve months.

7. Glaucoma was present in 2 of the 11 patients in this series. It appears not rarely in association with malignant exophthalmos and is usually improved by control of the exophthalmos.

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GROWTH HORMONE AND EXPERIMENTAL DIABETES*

F. G. YOUNG, D.Sc.

From the Biochemical Laboratory, University of Cambridge, Cambridge, England

THE diabetogenic action of purified preparations of the anterior pituitary growth hormone in normal (1, 2, 3) and in partially depancreatized (4, 5) animals is now well attested. Whether or not this effect is produced by growth hormone uncontaminated by other pituitary hormones is still uncertain, and, in the present unsatisfactory state of knowledge concerning the criteria of purity of proteins, it would be unwise to assume that our best preparations of growth hormone are indeed free from physiologically significant amounts of other substances. The possibility that traces of adrenocorticotropin may be present in our preparations of growth hormone and may play a vital role in the etiology of growth-hormone induced diabetes cannot at present be ruled out.

Evidence that the secretion of extra insulin by the pancreatic islets is a condition for the exertion of the normal growth-promoting activity of growth hormone in higher animals is circumstantial and perhaps inconclusive, although we nevertheless believe that such is the case. It is, however, clear that some retention of nitrogen can occur under the influence of pituitary extracts in normal animals in circumstances where the secretion of extra insulin cannot take place (3, 6). Such evidence does not contradict the view that a rise in the rate at which insulin is secreted by the pancreas does take place when growth hormone is administered to an animal possessing pancreatic islet tissue. The fact that a fall in blood sugar level may sometimes be encountered as the result of the administration of growth hormone to animals possessing islet tissue (4, 7, 8) suggests the possibility that either the growth hormone acts directly on the islets to stimulate the secretion of insulin or, more probably, the action of growth hormone in antagonizing the peripheral action of insulin may cause insulin to be utilized in the tissues at such an abnormally high rate that the level of insulin in the blood falls. This fall in blood insulin concentration may itself stimulate the secretion of insulin by the pancreatic islets. Such a hypothesis agrees with the fact that the blood sugar level does not rise during the first few days of the daily administration of a diabetogenic growth-pro-

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moting anterior pituitary extract to a normal dog or cat, although during this latent period the rate of secretion of insulin by the pancreatic islets may be ten to twenty times the normal value (9).

The normal rat never becomes diabetic when treated with large doses of growth hormone, but always grows instead. We have given senile male rats, weighing around 400 grams and fed on a diet of meat, the equivalent of 100–150 milligrams of growth hormone per day without inducing diabetes, these animals being able to respond perfectly well to the pituitary growth stimulus even at their great age. Conversely, we have observed that when rats are treated with diabetogenic growth-promoting pituitary extract daily (equivalent to 1–2 mg. per day of growth hormone) from the day of weaning onwards for nearly a year, extra growth but no diabetes occurs. When the greater part of the pancreas of the rat is surgically removed at a preliminary operation, sufficient islet tissue remaining to prevent the appearance of pancreatic diabetes, then rats of some strains, but not of those available to us, become responsive to the diabetogenic action of growth hormone (4).

Diabetogenic growth-promoting anterior pituitary extracts induce extra growth and not diabetes in growing puppies and kittens, even when daily doses of the extract are administered which are highly diabetogenic in adult dogs and cats (9, 10, 11). In our experiments a proportion of the long-treated puppies did ultimately develop diabetes, and in these animals the pituitary-induced growth first declined and then stopped, as the diabetes rose in intensity. Nevertheless, if insulin were then given in addition to the pituitary extract, in amount sufficient to bring the diabetic condition under control, growth was resumed (9).

The results of experiments, both with the rat and with the dog, support the view that extra secretion of insulin by the pancreas occurs when growth hormone is administered to an animal and that it is only when the pancreas is thus called upon to provide extra insulin beyond its capacity to do so that diabetes develops.

In the adult dog or cat treated with growth hormone, there occurs a retention of nitrogen and an initial rise in body weight which takes place before the diabetic condition develops. After three to six days of treatment with growth hormone, at the time when the blood sugar level rises and diabetes develops, the upward trend of the weight curve may cease even though the retention of nitrogen continues. It is not unreasonable to suppose that the initial growth response to the treatment has not been maintained owing to an inability of the pancreatic islets to furnish the necessary amount of extra insulin, and that the physiologic phenomenon of growth has dissolved, under these conditions, into a pathologic condition of diabetes. In general terms we may say that if an animal can

grow in response to the stimulus exerted by pituitary growth hormone, as is true of the rat at all ages and of young puppies and kittens, then extra growth and not diabetes will develop. But in adult animals, such as the dog, the cat and the ferret, an excessive stimulation of those processes which initially induce extra growth under conditions in which such growth cannot be long maintained, leads ultimately to the pathologic outcome of diabetes, provided that the amount of food consumed by the animal suffers no serious diminution.

Although the capacity of the pancreas to secrete extra insulin in response to treatment with growth hormone is of importance, it is not the only factor in determining whether the animal becomes diabetic or bigger when treated with growth hormone. Obviously the amount and nature of the food is of great significance, and the question of whether or not the animal has the capacity to deposit extra tissue for the period of duration of the growth stimulus is also of importance. Thus, because the epiphyses of most of its bones are united, the adult animal usually cannot expand and put on extra weight for very long in response to a pituitary growth stimulus. It is clearly of relevant interest that diabetogenic growth-promoting anterior pituitary extracts do not induce diabetes in pregnant bitches (12, 13), or in pregnant cats (13). Youth and pregnancy share the privilege of being conditions in which the sustained deposition of extra tissue is possible, either as growth of the body of the young animal or as growth of the fetus in the uterus. There is, in fact, good evidence that growth-hormone treatment of the pregnant rat is associated with abnormally large offspring (14, 15) under conditions where the period of gestation is not lengthened, but unfortunately the variability of the size of the litter in the dog and in the cat has so far precluded our drawing similar conclusions with respect to our experiments with pregnant bitches and cats. The well-confirmed observations of Miller, Hurwitz and Kuder (16), that in the human being the tendency for diabetic mothers to produce large babies may be observed many years before overt diabetes develops, is of great interest in this connection and the experimental observations with animals support the view that both the large babies and the diabetic condition of the human mothers may result from a slight but sustained over-secretion of pituitary growth hormone.

If, in a lactating animal, one assumes that the metabolic processes involved in the growth of the nursing young are subsumed under those of the mother by way of the secreted milk, then two corollaries follow: a) lactating animals should be less likely to become diabetic when treated with growth hormone than normal ones; b) the administration of growth hormone to a lactating animal might be expected, under suitable conditions, to lead to an increase in the existing milk flow. In agreement with

the first possibility we found some years ago that lactating cats do not become diabetic when treated with large doses of diabetogenic growth-promoting pituitary extract (13). In agreement with the second possibility, we have recently observed that the administration of purified growth hormone to cows in declining lactation leads to an enhanced flow of milk (17); in other words, purified growth hormone is galactopoietic (18). It is interesting to recall that, in our earlier work concerning the galactopoietic activity of anterior pituitary extracts, Dr. Folley and the author (unpublished observations) found that the rise in milk yield of first-calf heifers was much less striking than that of older animals, but we were unable to determine whether the heifers had exhibited the alternative response of an increase in body weight as the result of the treatment.

Treatment of the lactating rat with growth-promoting anterior pituitary extract leads to growth of the mother without any significant indication of an enhanced flow of milk (19). The fact that the epiphyses of the rat are unclosed at all ages renders this species of animal more prone to grow in response to treatment with growth hormone than to exhibit the alternative responses to such treatment which we have discussed above. This being so, one might expect to observe more easily in the rat than in many other species, evidence for the putative naturally increased rate of secretion of pituitary growth hormone during pregnancy and lactation, in the shape of a stimulus to the growth of the mother. Cole and Hart (20) state that, in the rat, normal pregnancy stimulates the growth of the body of the mother and that this extra weight is not completely lost either during lactation or subsequently. In our own experiments, untreated lactating rats appeared to show, during the period of lactation, a significantly greater growth rate than did control nonlactating rats of a similar weight (19). We believe that it is probable that an enhanced secretion of growth hormone by the anterior pituitary gland may normally occur during pregnancy and lactation, and that certain of the skeletal changes sometimes observed in pregnant women may be attributed to this phenomenon.

Growth, including fetal growth, and milk production, are processes which involve a depression of the oxidation of carbohydrate and of protein. They all involve the maintenance of a positive nitrogen balance, even in an adult animal which was previously in nitrogen equilibrium, and can all, in some circumstances at least, be stimulated by pituitary growth hormone. Growth-hormone induced diabetes may be regarded as a type of overflow release, effective in some species. By this means, the material which has had its oxidation depressed as a preliminary step towards the laying down of new tissue or the formation of extra milk under physiologic conditions, may, under conditions in which these physiologic processes are frustrated, be partly converted to glucose and

excreted. It is interesting to recall in this connection an experiment by Paul Bert in 1884 (21) in which the udders were removed from a goat which later became pregnant. At parturition, the animal was observed to become temporarily diabetic. In this instance the suppression of the means whereby the physiologic process of milk secretion could realize itself led to a temporary diabetes.

CONCLUSION

In general, we may conclude that the depression of oxidative processes brought about by the growth hormone may, in circumstances in which the normal physiologic result of the stimulus cannot be realized or sustained, lead to the pathologic outcome of diabetes. In the diabetic condition the material, or its equivalent, which has had its oxidation depressed, is partly excreted in the form of unoxidized glucose.

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PITUITARY NECROSIS AND DIABETES MELLITUS

EUGENE R. MARZULLO, M.D. AND
MILTON B. HANDELSMAN, M.D.

From the Department of Medicine, Long Island College Hospital and the State University Medical Center at New York City College of Medicine, New York, N. Y.

THIS article deals with a case of diabetes mellitus and hypertension associated with pituitary necrosis and hypopituitarism. Experimentally, it has been established that the anterior pituitary and adrenal hormones have an important influence on carbohydrate metabolism. It is rare for the clinician to have an opportunity to study some of the laboratory phenomena occurring as a result of diseases of these glands. The effects of the overfunctioning pituitary and adrenal glands on carbohydrate metabolism have been studied in patients with acromegaly and with Cushing's syndrome, in whom diabetes mellitus is commonly found as a sequela. There are also reports of the diabetes resulting from these diseases being corrected by treating the overfunctioning gland. In a patient with basophilic adenoma, Cushing (1) was able to effect the disappearance of the diabetes by x-ray therapy to the skull. Almy and Shorr (2) studied the disappearance of established diabetes in an acromegalic, following basilar meningitis. Sprague *et al.* (3) reported a case in which the diabetes disappeared after the removal of an adrenal cortical tumor.

Reports concerning the effects of underfunction of the pituitary and adrenal glands in patients suffering from diabetes mellitus are uncommon. A recent review (4) discloses only 22 cases reported with coexisting diabetes mellitus and Addison's disease. Feldman *et al.* (5) in 1947 could find only 3 cases of hypopituitarism occurring in diabetes and he added a fourth case. Since then, Vandenbroeck and Ferin (6) have reported a fifth case. The following is a report of a sixth case of pituitary necrosis and diabetes mellitus:

CASE HISTORY

Clinical data

Case #35363: This man was a 53-year-old nickelplater.

First hospital admission: August 17, 1942 to September 9, 1942.

Chief complaint: Progressive blurring of vision of ten months' duration.

Present illness: The patient was well until ten months previously, when he began to notice a "fogging" of vision. Eye glasses prescribed by an optometrist were of no benefit. Four months later an ophthalmologist was consulted and the patient was advised to have a general physical checkup. He was reported to have been normal

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upon physical examination. He entered the hospital because his vision continued to fail.

He had recently lost 10 pounds in weight despite a good appetite. There was nocturia (×4–5), and polyuria for several months previous to hospital admission.

Physical examination: He was well developed and well nourished and in no acute distress. The temporal arteries were tortuous and were easily seen as prominent vessels. His eyes were large and prominent but not truly exophthalmic. Extraocular movements were normal. The eye grounds revealed bilaterally many white spotty exudates scattered throughout. Small linear hemorrhages were also seen. The arteries were narrow and tortuous. The optic discs were normal. The thyroid was not palpable. The heart was not enlarged to percussion and no murmurs were heard. The radial and brachial arteries were hard and tortuous. The leg arteries were normal to palpation. The blood pressure was 200/90 on admission and 155/85 on the second day. There was a normal male distribution of hair. The external genitalia were normal in appearance. General neurologic examination did not reveal anything abnormal.

Laboratory data: August 17, 1942, Urine: specific gravity 1,037; glucose 3+; acetone 2+; albumin 0; microscopic examination noncontributory. Blood chemistry: fasting blood glucose 260 mg. per cent; urea nitrogen 13.4 mg. per cent; CO_2 content 46 vol. per cent.

Clinical impression: 1) Diabetes mellitus; 2) diabetic retinopathy; 3) generalized arteriosclerosis; and 4) essential hypertension.

Course: On admission, August 17, 1942, the patient was given a diet consisting of C_{200} P_{100} F_{70}, with 25 units of unmodified insulin three times daily before meals. On this regimen his urine was free of glucose most of the time and by August 27 his fasting blood sugar was 196 mg. per cent. He was then given 30 units of protamine zinc insulin with an additional injection of 10 units of regular insulin separately before breakfast. The glycosuria disappeared. On the day of discharge, September 9, 1942, his fasting blood glucose was 111 mg. per cent. At no time did the patient have an insulin reaction.

Interval note: Since discharge the patient had not adhered to a regulated regimen. He had generally restricted his starch intake and had taken 40 units of unmodified insulin daily. His vision was still seriously impaired.

Second hospital admission: November 27, 1943 to December 17, 1943. The patient was readmitted to the hospital on November 27, 1943, because of fever and cough. Nine days previously he had had a severe rhinitis and nonproductive cough. A diagnosis of "grippe" had been made. The cough became worse and he had a remittent fever reaching as high as 103°. On the day before admission rales were found in his chest bilaterally and his blood pressure was 110/70.

Physical examination revealed that the patient was well nourished. He was acutely ill and dyspneic, with a fever of 104° and a pulse rate of 120 per minute. The respirations were 32 per minute. He was moderately dehydrated and somewhat disoriented. The right chest was dull to percussion posteriorly and on auscultation tubular breathing and many crepitant rales were heard throughout the entire right side.

Laboratory data: November 27, 1943. Blood Count: R.B.C. 3.65 million; Hgb. 12 Gm. W.B.C. 30,300; differential, P. 97 per cent, S.L. 2 per cent, L.M. 1 per cent. Urine: specific gravity 1,020; glucose 3+. Blood chemistry: urea nitrogen 32.8 mg. per cent; CO_2 content 30 vol. per cent. Sputum: culture and direct smear typing revealed pneumococcus, type III.

X-ray examination of the chest revealed the heart to be normal in size and position. There was consolidation of the right upper lobe associated with encapsulation of fluid above the interlobar septum. The right diaphragm was elevated.

The electrocardiogram showed sinus tachycardia and left axis deviation but otherwise the result was normal.

Clinical diagnosis: 1) Lobar pneumonia, type III, in the right upper and lower lobes; 2) diabetes mellitus; and 3) diabetic retinopathy.

Course: The patient was given 2 grams of sulfadiazine and 1 gram of bicarbonate of soda every four hours for eight and one-half days. His temperature dropped gradually so that on the third day it was 100.4° and after the seventh day it was normal. The signs of consolidation disappeared rapidly so that five days after admission very few signs were present.

Summary of treatment of diabetes:

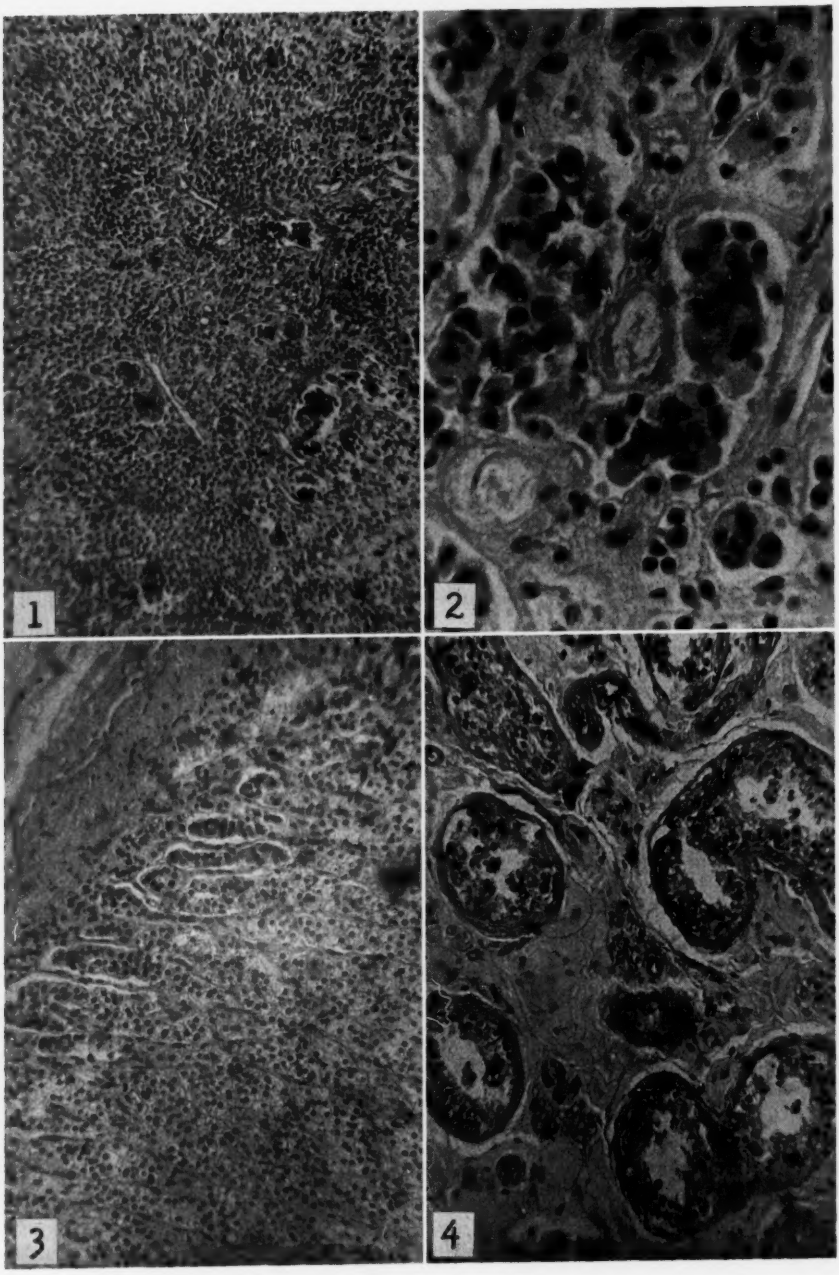
Date	Blood glucose, mg. %	Blood CO_2, vol. %	Range of urinary glucose	Insulin, u./24 hrs.
11-27-43	459	30	2+ to 4+	165
11-28-43	—	50.4	4+ to 2+	120
11-29-43	—	—	2+ to 0	100
11-30-43	—	—	0 to 1+	30
12- 1-43	insulin reaction		0 to 0	30

The insulin reaction was mild and it was quickly relieved by orange juice. Diabetic regulation was subsequently easily attained with a diet of C_{250} P_{90} F_{90} and 40 units of protamine zinc insulin each morning. On this regimen his urine specimens were practically always free of glucose and his postabsorptive blood glucose was 95 mg. per cent. His blood pressure, taken daily, ranged from 140/80 to 120/60. He was discharged on December 17, 1943.

Third hospital admission: February 3, 1944, until death on February 28, 1944. The patient was readmitted because of loss of appetite and weakness. Following discharge from the hospital two and a half weeks previously the patient noticed that his appetite, which in the hospital had been ravenous, became progressively poor. The insulin dosage was markedly reduced by his local physician, because the patient refused food. During the week before admission his appetite completely disappeared and he had bouts of nausea with vomiting. He was extremely weak and his blood pressure was found to be 90 systolic.

Physical examination on this admission revealed poor nutrition for the first time, and evidences of chronic illness. He was not in acute distress. His temperature was 98.6°, pulse 80, respirations 20 per minute, and blood pressure 100/70. There was a papular-pustular rash over his forehead, cheeks and chest but no other abnormal physical findings. There was no change in the amount of hair nor in its distribution.

Laboratory data: February 3, 1944, Blood count: R.B.C. 3.56 million; Hgb. 11 Gm.; W.B.C. 7,850; differential, P. 52 per cent; S. L. 40 per cent; L.M. 7 per cent; sedimentation rate 118 mm. per hour. Urine: specific gravity 1,005; albumin 0; sugar 0; acetone 0; normal on microscopic examination. Blood chemistry: glucose 88 mg. per cent; urea nitrogen 9.4 mg. per cent; total protein 6.3 Gm. per cent; albumin 3.6 Gm per cent; globulin 2.7 Gm. per cent; cholesterol 233 mg. per cent; cholesterol esters 147 mg. per cent; icterus index 4 units; cephalin cholesterol flocculation test, negative results; alkaline phosphatase 8.9 units; serum sodium 345 mg. per cent (normal, 325 to 340);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serum chlorides 520 mg. per cent; and serum potassium 21.6 mg. per cent (normal, 16.0 to 22.0).

The electrocardiogram showed a rate of 70 per minute, the PR interval was 0.18, QSR was slurred, and there were T waves of low voltage in all leads.

Glucose tolerance test: After ingestion of 100 Gm. of glucose, the blood glucose was: fasting, 88 mg. per cent; first hour, 170 mg.; second hour, 224 mg.; and third hour, 214 mg. per cent. The glucose tolerance test was repeated on February 9, 1944 with two doses of glucose, 50 grams each. The results were as follows: fasting blood glucose, 74 mg. per cent; one-half hour after second dose, 150 mg.; second hour, 207 mg.; third hour, 230 mg.; fourth hour, 242 mg.; fifth hour, 256 mg.; sixth hour, 208 mg.; and seventh hour, 164 mg. per cent.

Course: During the first two days of hospitalization the patient seemed brighter and he began to take moderate quantities of food without vomiting. His complaint was chiefly "general fatigue." Despite the absence of insulin therapy, no glucose appeared in his urine, even after 1,000 cc. of 5 per cent glucose in saline had been given intravenously. His blood pressure fell to 80/60.

On the following day 5 mg. of desoxycorticosterone was started and given daily thereafter. Liver extract and vitamin B complex were also given parenterally. This treatment was continued for two weeks. During this time the patient was afebrile. His illness was characterized by weakness, and occasional periods of drowsiness, anorexia and vomiting. His diet was selected without regard for its carbohydrate content and included a large amount of meat, eggs and milk. Mental depression developed, with anxiety about death. There was no glycosuria at any time. Two morning fasting blood glucose values were 64 and 66 mg. per cent. The serum potassium remained normal. The fluid intake and output were not remarkable. The blood pressure reached a maximum of 128/72 without any change in his clinical condition. On February 24, 1944, he complained of severe pain in his left ear. An otolaryngologic consultation showed nothing abnormal. An ophthalmologic consultation revealed that cataracts had developed since his last hospitalization, so that studies of the fundi were impossible. The pain in the left ear persisted until February 26, when the patient had several chills followed by a rise in temperature to 101°. The rise continued to 105° on February 28. The urine was normal. A blood culture showed no organisms. A blood count showed W.B.C. 8,000, with P. 73 per cent, S.L. 26 per cent, and L.M. 1 per cent. The CO_2 content of the plasma was 43.8 vol. per cent. The patient expired in coma.

Anatomic findings

Autopsy No. 3407 (Dr. Richard Ferayorni). The body was that of a well developed, poorly nourished white male. The head was covered with abundant black hair. There was no pigmentation of the gums or mucous membranes. The chest was covered by abundant coarse black hair. The abdomen was also covered by abundant black hair with

FIG. 1. *Anterior lobe of the pituitary* (L. P.). The gland is fibrous with many areas of necrosis infiltrated with polymorphonuclear leucocytes, plasma and other cells. Small islets of secretory cells are present.

FIG. 2. *Anterior lobe of the pituitary* (H.P.). The remaining islets of secretory pituitary cells contain eosinophilic, basophilic and neutrophilic cells.

FIG. 3. *Adrenal cortex* (L.P.). The cortex is thin and the cords somewhat small, but the general architecture is normal.

FIG. 4. *Testis.* (H.P.). Spermatogenesis is markedly reduced. Appreciable thickening of the basement membrane of the tubules is present.

normal male distribution. The external genitalia were normal in appearance; both testes were small. The panniculus adiposis measured 2 cm. in thickness and was yellow.

Heart: Weight, 335 grams. There were mild atheromatous changes on the intimal surfaces.

Lungs: The lower portion of the right upper lobe and the upper portion of the right lower lobe showed thick fibrous adhesions. This area was quite solid and had a brownish discoloration. On section, the consolidated area reveals a mottled grayish-brown firm parenchyma with thick strands of white fibrous tissue running through it. Otherwise the lungs were normal.

Liver: Grossly, the liver seemed normal. Microscopically, the central vein areas were slightly distended and engorged with erythrocytes. There was some atrophy of the liver about these areas. There were several foci of necrosis with lymphocytic infiltration in the parenchyma.

Pituitary: This was removed from a slightly enlarged sella turcica. The internal carotid arteries were firmly attached to each lateral pole of the gland and were patent. There were no adhesions about the gland, which was enlarged and oval. The capsule was gray, smooth and thickened and the gland had a cystic feel. Section revealed a central cavity in the anterior lobe, approximately 4 mm. in diameter, which was lined by a softened grayish-brown granular layer of necrotic pituitary substance. The cavity was free of exudate. At the periphery of the cut section there was another layer of white firmer tissue which lay close to the gland capsule and was 3 mm. thick. There was thickening of the meninges at the base of the brain. Microscopically, the entire architecture of the pituitary was distorted. There was an irregular central cavity which was empty but its wall was necrotic and fragmented. The gland was mainly fibrous with small areas of necrosis (Fig. 1). There were only three or four small groups or islands of secretory cells. These islands contained the usual proportions of chromophobe, acidophil and basophil cells (Fig. 2). Many of the cells were detached from the cords and lay free. They had a spherical shape and abundant cytoplasm, which often contained many small vacuoles. Much of the tissue close to the cavity was fragmented and poorly vascularized and there was much fibrous tissue which extended to the periphery. This fibrous tissue was heavily infiltrated with polymorphonuclear leucocytes, plasma cells, lymphocytes, large mononuclear cells and some large histiocytes loaded with fat. In some areas there was beginning organization with proliferation of fibroblasts and capillaries, whereas in other areas the fibrosis was dense. Just beneath the fibrous capsule in the anterior lobe there was a small arteriole which was completely thrombosed and canalized with three small capillaries within its organized lumen. Adjacent to this arteriole there was a smaller one with a lumen narrowed by a thickened wall. There was a small violaceous lamellated body lying in a branching cleft of the abscess cavity. The center was vacuolated and hyaline and was surrounded by concentric fine wavy rings of basophilic staining material. The outermost ring was more acidophilic and stained more intensely than the rest. There were other smaller lamellated psammoma bodies in a fibrous part of the gland.

Adrenals: These were grossly normal in size and shape. On section, the cortex was thin, bright yellow, and was separated from the pearly gray medulla in some areas by a dark red intermediate zone. Microscopically, the adrenal cortex was somewhat thin; the cords were small and atrophic (Fig. 3). There was an abundant amount of lipoid within the zona fasciculata and zona reticularis. In the medulla there were several small accumulations of lymphocytes and chromaffinity was readily noted. The periadrenal tissues were densely fibrous.

Pancreas: Length, 19 cm. There were no areas of necrosis or hemorrhage. There

were diffuse increases in fibrous tissue among the acini. The islands of Langerhans were few in number but were normal in size.

Thyroid: The left lobe was slightly enlarged and contained a spherical adenoma measuring 2 cm. in diameter at its lower pole. On sectioning, the parenchyma seemed normal in appearance. The acini varied somewhat in size and were lined by flattened epithelium. There was an abundant amount of colloid within the acini. There was a generalized increase in the fibrous tissue.

Parathyroids: These were orange-brown in color and the left superior parathyroid was slightly enlarged, measuring 5×3×1 mm. Under the microscope, numerous cords were seen which were separated widely by deposits of fat. There was a normal number of oxyphil and chief cells within the cords. The cells were plump and showed no signs of degeneration.

Testes: These were symmetrical, soft, and on section revealed a yellowish orange parenchyma from which the tubules were easily strung. Spermatogenesis was markedly reduced; only a few degenerating spermatids were seen in occasional tubules (Fig. 4).

Bone marrow (vertebral): The bony trabeculae were thin and delicate and had a normal osseous structure. The marrow contained abundant megakaryocytes and erythropoietic cells. There was a marked increase in the number of immature eosinophils. The remainder of the myeloid series appeared normal.

Brain, prostate and kidneys were essentially normal.

The final pathologic diagnoses were: 1) Pituitary necrosis; 2) lobar pneumonia (organized); 3) atrophy of the testes; 4) chronic passive congestion of the liver with focal necrosis.

COMMENT

The clinical course of this patient after he recovered from pneumonia follows the pattern found in Houssay's experimental animals in which hypophysectomy was performed after pancreatectomy. There was a rapid amelioration of the diabetes, the glycosuria disappeared and a tendency to insulin reactions developed. The patient had marked anorexia and asthenia almost from the onset. The significance of this sequence of events was not appreciated until later. Despite discontinuance of insulin therapy there were recurring transient episodes of syncope and sweating, which were severe enough to suggest to the attending physician the possibility that a coronary occlusion had occurred. Electrocardiography ruled this out. Ketonuria did not occur despite starvation and the discontinuance of insulin.

Long and his coworkers (7) have reported similar results in depancreatized animals after bilateral adrenalectomy, but clinical reviews concerning Addison's disease occurring in patients with diabetes mellitus do not often report amelioration of the diabetes to such a full degree. The glycosuria in patients with Addison's disease does not completely disappear; and despite the increased sensitivity to insulin, the insulin requirement of of most of the patients does not drop, or drops comparatively little. This is in direct contrast to the findings in 5 of the 6 cases of hypopituitarism occurring in association with diabetes. In these patients the

amelioration of the diabetes was comparable to that found in hypophysectomized depancreatized animals.

Review of reported cases

The 6 reported cases of diabetes mellitus with subsequent destructive disease of the pituitary, which were available for analysis, made it possible to study the Houssay phenomenon in humans. The first 2 reported cases presenting this phenomenon occurred in what may be considered as a benign and chronic form.

Not much information is given concerning the first patient (Case I) reported by Calder (8) in 1932. The author mentions that there was a preceding diabetic type of glucose tolerance curve, which returned to normal following the onset of asthenia, loss of weight and diminished sexual function. The hypopituitary nature of this man's illness was demonstrated by laboratory tests. With treatment, he improved sufficiently to return to work and the diabetes did not recur.

The patient (Case II) reported by Lyall and Innes (9) in 1935 was a 28-year-old man who had diabetes for two years and required 80 units of insulin daily. Over a period of six months the diabetes was ameliorated so that insulin therapy could be stopped. X-ray studies revealed evidence of a tumor in the region of the pituitary with a dense deposit lying under the sella turcica. This patient, too, continued to live.

The next 2 cases can be classified as the acute or subacute form of the Houssay phenomenon.

Kotte and Vonderahe (10) in 1940 reported a 40-year-old diabetic (Case III) who was known to have had diabetes for five years. This patient dieted and took insulin sporadically when he had glycosuria. For two months before his death he had been moderately ill but the clinical picture changed radically in the last two weeks of that period. During this latter phase he complained of headache, asthenia and lethargy but he continued to work until three days before his death. Two days before hospitalization his urine contained excessive glucose, despite the fact that his food consumption had been negligible. He was hospitalized on the day of his death. On admission his blood sugar was 31 mg. per cent, dropping to 20 mg. per cent twelve hours later. At necropsy there was found a massive infarction with necrosis of the glandular portion of the anterior hypophysis. This was of recent origin. In addition, there was miliary and caseating tuberculosis of the lungs and acute ileitis. In this case the adrenals and pancreas did not seem to be abnormal.

The fourth case (Case IV), reported by Feldman *et al.* (5) in 1947, was a 50-year-old married woman. Unfortunately, no mention is made as to whether she had ever been pregnant. The patient's diabetes was diagnosed

twelve years previously, at which time it was stabilized with 35 units of insulin daily. She subsequently took a daily dose of 20 units sporadically for three more years. After this she discontinued insulin therapy but showed glycosuria until one year before the period of observation. She was in the hospital for the last three and one-half months of this period. The clinical course was characterized by headaches, asthenia, anorexia, vomiting and and a mental picture varying from indifference to a puerile attitude. Later she had severe orthostatic hypotension and hypoglycemic crises. The patient was treated with a high sodium diet and 5 cc. of adrenal cortical hormone daily without much clinical improvement. She eventually died in hypoglycemic crisis, despite intravenous glucose therapy. At autopsy, four-fifths of the pituitary showed hyaline degeneration described by the authors as similar in appearance to the necrosis found in large aortic atheromata with cholesterol clefts. The adrenals were smaller than normal and microscopically there was interstitial fibrosis. The pancreas showed normal islets of Langerhans.

The patient (Case V) reported by Vandenbroeck and Ferin (6) was studied carefully only at the onset of the illness. Diabetes mellitus was diagnosed when she was 28 years old and was stabilized on a regimen requiring 34 units of insulin before breakfast and 26 units before the evening meal. Four years later she was married and after one year she miscarried in the sixth month. She had had headaches for one month. Following this she began to have repeated hypoglycemic episodes. The diabetes was restabilized with an insulin dose of 25 units before breakfast and 18 units before the evening meal. There was a decrease in the axillary and pubic hair. The breasts did not become engorged in the postpartum period and menstruation did not return. Six months later her diabetic status was unchanged, she had lost 5 kilograms in weight, the B.M.R. was −12 per cent and the blood pressure was 135/100. Her genitalia were found to be atrophied. Endometrial biopsy and vaginal smear studies showed lack of ovarian activity. This case fulfilled the criteria established by Sheehan (11) for the diagnosis of postpartum pituitary necrosis. Pregnant mares' serum was tried on three occasions and stimulated sexual functions without influencing the diabetes. The patient changed physicians but the authors learned that she died in hypoglycemic crisis two and one-half years after the onset and that terminally the diabetes was "untreatable."

Hypopituitarism in patients with diabetes mellitus

In general, the cases just reviewed presented the same clinical features seen in patients with hypopituitarism, with the addition of the Houssay phenomenon. The amelioration of the diabetes, with the exception of Case III, appeared as one of the earliest signs. It was sufficiently complete to

allow a regular diet and the cessation of insulin therapy in all except Case V. In this case, the subsequent course was not directly observed. However, despite the marked improvement in the diabetes, the general status of carbohydrate regulation in 4 of the 6 patients was impaired in the fashion that Russell (12) has emphasized as occurring in hypopituitary experimental animals. In Houssay animals, starvation and small doses of insulin bring on severe hypoglycemia. The lability of glucose homeostasis is illustrated in the human cases. Three of the 4 deaths described in this review were precipitated by a hypoglycemic crisis. In our case, increased insulin sensitivity was noted early in the course. The result of the glucose tolerance test performed on this patient three weeks after the diabetes mellitus had clinically disappeared, was further illustrative of the instability of carbohydrate homeostasis. After glucose administration, the blood glucose remained at normal levels for two hours and then rose to diabetic levels, where it remained for five hours despite fasting.

Soskin (13) has shown that the feeding of protein and endogenous protein (but not fat) can raise the blood sugar in Houssay animals to hyperglycemic levels. This raises speculations regarding the glycosuria found in Kotte and Vonderahe's patient (Case III) thirty-two hours before death, although the clinical history suggests that the pituitary lesion was about two weeks old. Since this patient had an active tuberculosis, producing sepsis, which is known to increase body protein metabolism, the possibility exists that the glycosuria arose from endogenous protein. A similar phenomenon was reported by Chabanier *et al.* (14), who performed a surgical ablation of the pituitary in a patient with severe diabetes, leading to an amelioration of the diabetes. However, soon after the operation there was a reactivation of this patient's tuberculosis and the diabetes became worse. The role of infection in aggravating the diabetic condition in Houssay patients and animals requires further study

The possible effects of protein therapy in preventing fatal hypoglycemia deserves special consideration, inasmuch as acute pituitary failure does not lead to sudden death. Three of the 4 patients who died succumbed at varying times later, in hypoglycemic crisis. Severe hypoglycemia did not occur in our patient when he was in the hospital. This exception might have been due to the fact that he received protein-containing foods as well as carbohydrate-rich foods, these being forcibly fed by a nurse specially instructed to do so.

Two of the 6 reported patients (Cases IV, VI) were treated (with salt and desoxycorticosterone) for Addison's disease. The hypotension improved slightly but the general condition of both patients remained unchanged.

One of the patients (Case V) presented the features seen in postpartum

pituitary necrosis. Administration of pregnant mare's serum stimulated endometrial growth in a previously atrophic uterus but did not influence the carbohydrate metabolism. This woman did not have hypotension.

SUMMARY

A male patient with diabetes mellitus and essential hypertension is reported, who was under constant medical observation. Pneumonia developed, following which there was a disappearance of his diabetes and hypertension. Death occurred after a short illness and pituitary necrosis was found at necropsy. A review of other cases of hypopituitarism occurring in patients with diabetes mellitus is included.

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The Association for the Study of Internal Secretions

THE 1951 ANNUAL MEETING

GENERAL INFORMATION

Headquarters: Chalfonte-Haddon Hall, Atlantic City, New Jersey

Registration: Everyone attending the meetings is required to register. By action of the Council, non-members will be charged a registration fee of $2.00 for any part of the scientific sessions. Members should present their current membership cards when registering. Admission will be by badge only.

The Scientific Sessions: Due to increasing the meeting to three days this year, all scientific sessions will not be held in the same room. Please refer to the daily program as to the location of each session. Programs will begin promptly on schedule. Presentation of papers at all sessions will be LIMITED TO TEN MINUTES and authors are requested to adhere strictly to this schedule. Manuscripts of all papers should be submitted to the presiding officer or to the Secretary-Treasurer at the end of the presentation.

Annual Dinner: The Annual Dinner of the Association will be held on Friday evening, June 8, at 7:30 P.M. in the Rutland Room of Chalfonte-Haddon Hall preceded by cocktails at 6:30 P.M. in the Benjamin West Room. Secure tickets at time of registration.

Local Arrangements: Dr. Matthew Molitch, 705 Pacific Avenue, Atlantic City, New Jersey, is in charge of the local arrangements for the meetings.

Secretary-Treasurer: Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma.

PROGRAM

THURSDAY, JUNE 7, 1951

8:30 A.M. Registration.—*Music Room*

I. 9:30 A.M. GENERAL SUBJECTS—*Music Room*

Chairmen: C. N. H. Long and Lawson Wilkins

1. Endocrine Studies on Inherited Obesity in the Mouse. *Robert S. Speirs* (introduced by R. K. Meyer).

2. Endocrinological Effects of Amphenone "B." *Roy Hertz, Milton J. Allen* (by invitation), and *W. W. Tullner* (by invitation).

3. Effect of Vitamin A and Compound L on the Thyroid, Adrenal and Lymphoid Tissue of the Rat. *William L. Money, Jean Fager* (by invitation), *Virgina Lucas* (by invitation), and *Rulon W. Rawson.*

4. Tracer Studies with Radioactively Labeled Prolactin Preparations. *Martin Sonenberg* (by invitation), *William L. Money, Albert S. Keston* (by invitation), *Patrick Fitzgerald* (by invitation) and *John T. Goodwin* (by invitation).

5. Effect of Prolactin on Phosphorus Metabolism of Pigeon Crop-Sac: Applicability to Bioassay of Prolactin. *Robert W. Brown* (by invitation), and *George Sayers.*

6. The Clinical Effect of Diethylstilbestrol on Osteoarthritis in Women. *Alton C. Grorud.*

7. A Syndrome, Distinct from Acromegaly, Characterized by Spontaneous Lactation, Amenorrhea, and Low Follicle-Stimulating Hormone Excretion. *Anne P. Forbes, Philip H. Henneman* (by invitation), *Grace C. Griswold* (by invitation), and *Fuller Albright.*

8. Studies on a Patient with Diabetes Insipidus and Adrenocortical Insufficiency. *Herbert Gershberg, Stephen Leslie,* and *Elaine P. Ralli.*

9. The Eosinophile Response to Stress of Patients with Surgically Produced Thalamic and Hypothalamic Lesions. *William H. Perloff, Lester M. Levy* (by invitation), and *Agamemnon Despopoulos.*

10. Steroidal Control of Cerebral Metabolism in Man. *R. C. Bentinck* (by invitation), *G. S. Gordan, J. E. Adams* (by invitation), and *T. B. Leake* (by invitation).

11. Dual Control of ACTH Release. *Claude Fortier* (introduced by Hans Selye).

12. Hormonal Regulation of Phagocytosis *Paola S. Timiras* (introduced by Hans Selye).

13. Metabolic and Endocrine Changes Associated with Hypoglycemia. *H. P. Taft, Max Miller, William R. Drucker,* and *James W. Craig* (introduced by Hans Hirschmann).

14. Inhibition of the Gametokinetic Response in Male "Rana Pipiens" with Adrenolytic Drugs. *Sarah L. Clark* (by invitation), *Robert B. Greenblatt,* and *Robert M. West* (by invitation).

II. 2:00 P.M. PRESIDENTIAL ADDRESS—*Music Room*

President Edward H. Rynearson: "Controlled Observations in the Treatment of Patients."

III. 2:30 P.M. PITUITARY AND ADRENAL GLANDS—*Music Room*

Chairmen: J. S. L. Browne and Jane A. Russell

15. Effect of Hypophyseal Growth Hormone (GH) on the Thiocyanate Space and Muscle Electrolytes. *Adrienne Applegarth Batts* (by invitation), and *Leslie L. Bennett.*

16. Hyperglycemia and Glycosuria in the Forced-Fed Rat Receiving ACTH and Anterior Pituitary Growth Hormone. *Frank L. Engel, A. Viau* (by invitation), *W. J. Coggins* (by invitation), and *W. Lynn* (by invitation).

17. Variations in Cathepsin Activity of Rat Tissues Induced by Hypophysectomy and Replacement Therapy. *James C. Mathies* (by invitation), and *Oliver H. Gaebler.*

18. Effect of Pituitary Hormones on Nerve Function. *Clara Torda,* and *Harold G. Wolff* (introduced by Ephraim Shorr).

19. Some Hormonal Aspects of Water Excretion in Man. *Alexander Leaf,* and *Audley R. Mamby* (introduced by Fuller Albright).

20. Evaluation of the Responsiveness to Prolonged ACTH Dosage of a Patient with Panhypopituitarism. *Nelson H. Brown* (by invitation), and *R. B. Greenblatt.*

21. The Use of Cortisone in the Treatment of Young Infants with Congenital Hyperplasia and Defective Electrolyte Regulation. *John F. Crigler, Jr.* (by invitation), *Lytt Gardner, Claude J. Migeon* (by invitation), and *Lawson Wilkins.*

22. Accumulation of ACTH in Kidney. *John B. Richards* (by invitation), and *George Sayers.*

23. Effect of Varying Concentrations of ACTH and Growth Hormone upon Corticosteroid Release from Perfused Adrenals. *I. Macchini* (by invitation), *O. Hechter,* and *G. Pincus.*

24. The Nature of ACTH Resistance. *Peter H. Forsham, Albert E. Renold* (by invitation), and *Thomas F. Frawley* (by invitation).

IV. 8:00 P.M. INFORMATION PLEASE—*Music Room*

A program of informal discussion, E. H. Rynearson presiding.

FRIDAY, JUNE 8, 1951

8:30 A.M. Registration—*Viking Room*

V. 9:00 A.M. THYROID GLAND—*Viking Room*

Chairmen: Rulon W. Rawson and Robert H. Williams

25. Steps in the Secretion of the Thyroid Hormone. *C. P. Leblond.*

26. The Metabolic Fate of Radioactive Iodine in Thyroid Hyperplasia Versus Hyperfunction. *William T. Salter.*

27. Metabolism of Radiodiodotyrosine in the Human. *F. Raymond Keating, Jr.*

28. The Nature of the Blood Iodine Following Large Doses of I^{131}. *J. Robbins, D. V. Becker, and J. E. Rall* (introduced by Rulon W. Rawson).

29. Relationship of Gonadal Imbalance to Thyroid Disease—A Statistical Study. *Francis P. Ferrer,* and *Thomas H. McGavack.*

30. Ovarian Function in Thyrotoxicosis and Hypothyroidism. *Richard Goldsmith* (by invitation), *Sommers Sturgis* (by invitation), *John B. Stanbury* (by invitation), and *Jacob Lerman.*

31. Effect of Massive Cortisone Therapy on Thyroid Function. *D. S. Fredericksen* (introduced by Peter H. Forsham).

32. Modifications of TSH Action by ACTH and Cortisone in Hypophysectomized Rats. *Dixon M. Woodbury* (by invitation), *B. N. Ghosh,* and *George Sayers.*

33. Blood Thyroid and Thyrotrophic Hormone Levels in Endocrinopathy. *S. A. D'Angelo, K. E. Paschkis, A. Cantarow,* and *A. S. Gordon.*

34. A Comparison of the Effect of Thyrotrophin on Iodine Metabolism in

Euthyroid and Hyperthyroid Humans. *D. V. Becker, J. E. Rall,* and *W. C. Peacock* (introduced by Leonard P. Eliel).

35. Inhibition of Thyroid Function by Struma Ovarii: Effect of TSH on Normal and Inhibited Thyroid. *Martin Perlmutter, Shirley Weisenfeld, Eleanor A. Zucker* (by invitation), and *Stanley L. Slater* (by invitation).

36. The Effect of Hypophysectomy on Intrathyroidal Metabolism of I^{131}. *A. Albert.*

37. Pathological Characteristics of the Gland Prepared for Surgery with Iodo-Thiouracil and Other Anti-Thyroid Drugs. *Boris Catz* (by invitation), *Weldon K. Bullock* (by invitation), and *Paul Starr.*

38. Effects of Sodium Iodide, Propyl Thiouracil, and Methyl Mercaptomidazol During Radioiodine Therapy of Hyperthyroidism. *Howard Hamilton* (by invitation), and *Sidney Werner.*

VI. 2:00 P.M. GONADS AND REPRODUCTION—*Viking Room*

Chairmen: Earle T. Engle and E. C. Hamblen

39. Demonstration of a Non-Estrogenic Uterine Stimulating and Estrogen Augmenting Substance in Urine from Pregnant Mares. *Herman Cohen,* and *Robert W. Bates.*

40. Identification of Steroids in the Human Testis. *Joseph. W. Goldzieher,* and *Irene S. Roberts* (by invitation).

41. Studies on the Metabolism of Progesterone. *John G. Wisell* (introduced by Leo T. Samuels).

42. Uptake of P^{32} in Seminal Vesicles of Castrate Rats After Treatment with Testosterone Propionate. *Walter Fleischmann,* and *Susan Kann Fleischmann* (by invitation).

43. Effect of Purified Pituitary Gonadotrophins in the Hypophysectomized, Immature Male Rat. *C. A. Schaffenburg* (by invitation), and *E. P. McCullagh.*

44. The Acid Phosphate Concentration of the Prostatic Exprimate During Normal Puberty. *John Esben Kirk* (by invitation), *Albert Eisenstein* (by invitation), and *Cyril M. MacBryde.*

45. Some Metabolic Studies with 17-Methylandrostenediol. *Jonas Weissberg, Jacqueline E. Chevalley, Sidney Stern,* and *Thomas H. McGavack.*

46. Variations in Blood Lipids and Lipoproteins Throughout the Menstrual Cycle. *Hyman Engleberg* (introduced by Samuel Glass).

47. Klinfelter Syndrome: A Study in Five Cases. Histophysiologic Basis for a Pathogenic Interpretation. *F. A. de la Balze, F. C. Arrillaga* (by introduction), *J. Irazu* (by invitation), and *R. E. Mancini* (by invitation).

48. The Treatment of Uterine Bleeding by Intravenous Administration of Estrogen. *Robert B. Greenblatt,* and *W. E. Barfield* (by invitation).

49. The Effects of Chorionic Gonadotrophin and Luteotrophin on the Maintenance of Corpus Luteum Function. *Paul H. Fried,* and *A. E. Rakoff.*

50. Therapy of Eunuchoidism with Chorionic Gonadotropin: Aqueous Solution Compared with An Oil and Beeswax Suspension. *Frederic C. Bartter, Ronald Sniffen* (by invitation), *Fred Simmons* (by invitation), and *Fuller Albright.*

51. Increased Estrogen Excretion Due to Stimulation of Leydig Cells in Adult Men Receiving Chorionic Gonadotrophin. *William O. Maddock,* and *Warren O. Nelson.*

VII. ANNUAL DINNER, Friday, June 8, 1951.

Edward H. Rynearson, President, Presiding

6:30 P.M. **Cocktails,** *Benjamin West Room*
7:30 P.M. **Dinner,** *Rutland Room*

Presentation of Awards

SATURDAY, JUNE 9, 1951

VIII. 9:00 A.M. ADRENAL GLANDS—*Viking Room*

Chairmen: Gregory Pincus and George W. Thorn

52. Enzymic Hydrolysis of Urinary Corticoids. *Eleanor H. Venning.*

53. A Chemical Method for the Determination of Adrenal Steroids in Peripheral Blood of Human Patients. *Don H. Nelson* (by invitation), *Donald G. Willardson* (by invitation), *Frank H. Tyler,* and *Leo T. Samuels.*

54. Adrenal Cortical Function As Revealed by Histochemical Tetrazolium Studies. *B. W. Zweifach, M. M. Black,* and *E. Shorr.*

55. Observations on the Conversion of Cortisone to Other Corticosteroids. *Robert B. Burton, Christine Waterhouse* (by invitation), and *E. Henry Keutmann.*

56. The Inactivation of Cortisone by Tissue Slices. *Jean Louchart* (by invitation), and *Joseph W. Jailer.*

57. Incubation of Desoxycorticosterone and Other Adrenocortical Compounds with Various Surviving Tissues of the Rat. *John J. Schneider,* and *Patricia M. Horstmann* (introduced by W. M. Pearlman).

58. Influence of Adrenal Factors on Hexopoiesis in the Rat. *Albert S. Gordon, Sam J. Piliero* (by invitation), and *David Landau* (by invitation).

59. The Salivary Na/K Ratio and Adrenal Salt-Regulating Factors: Prolonged Salt Retention with Desoxycorticosterone Trimethyl-Acetate. *Thomas F. Frawley* (by invitation), and *Peter H. Forsham.*

60. Amino Acid Metabolism in Cushing's Syndrome and ACTH Induced Hyperadrenocorticism Using N-15 Incorporated in Glycine. *William Parson, K. R. Crispell* (by invitation), and *Arthur Ebbert, Jr.* (by invitation).

61. Studies in Fat Metabolism: The Effect of ACTH and of Steroid Hormones Upon the Ketosis Induced by the Feeding of a Pure Fat Diet to Human Subjects. *Laurance W. Kinsell, Sheldon Margen, Lenore Boling* (by invitation), *George D. Michaels* (by invitation), and *John W. Partridge* (by invitation).

62. Remission in Cushing's Syndrome After Bilateral Hemiadrenalectomy. *Herbert S. Kupperman. Arthur Bernstein* (by invitation), *Anne P. Forbes, Oliver Cope,* and *Fuller Albright.*

63. Endocrine Studies Following Bilateral Complete Adrenalectomy in Man. *George W. Thorn, Thomas F. Frawley, Peter H. Forsham,* and *D. Lawrence Wilson* (by invitation).

IX. 2:00 P.M. JOINT SESSION WITH THE AMERICAN DIABETES ASSOCIATION.—*Carolina Room*

Chairmen: E. H. Rynearson and Lester J. Palmer

64. Experimental Diabetes Produced by Dehydroascorbic Acid. *Joseph V. Princiotto* (introduced by Charles F. Morgan).

65. Changes in Serum Potassium During the Intravenous Glucose Tolerance Test. *D. Lawrence Wilson* (by invitation), and *George W. Thorn.*

66. The Effect of Cortisone on the Blood Glutathione Level. *Arnold Lazarrow.*

67. Amino Acids in Experimental Diabetes. *Smith Freeman.*

Intermission

68. The Banting Lecture: The Endocrine Control of the Blood Sugar. (40 min.) *C. N. H. Long,* Yale University Medical School, New Haven, Conn.

69. The Medical Aspects of Hyperinsulinism. *Penn G. Skillern* (by invitation), and *E. H. Rynearson.*

X. 4:30 P.M. Annual Business Meeting

To be Read by Title

70. Effect of Acute Stress Upon Blood Constituents, White Cells, and Urine Constituents in Normal Individuals. *W. James Kuhl, Jr.* (by invitation), and *Elaine P. Ralli.*

71. The Circulating Eosinophil Response of Mongoloids to Epinephrine. *Irving Rothchild,* and *John P. Riepenhoff* (by invitation).

72. Inhibition of the Adrenalinic Eosinopenia Due to Thiouracil Administration in Hyperthyroid and in Normal Human Subjects. *F. A. de la Balze, R. C. Mancini* (by invitation), *C. J. Scarpa* (by invitation), and *F. C. Arrillaga* (by invitation).

73. Turner's Syndrome Accompanied by Mongolism. Multiple Degenerative State. *Manuel M. Villaverde.*

74. Adipose Gynandrism. *S. Leonard Simpson.*

75. The Hypometabolic State: A Clinical Entity. *B. A. Watson.*

76. Influence of Growth Promoting Factors on Some Liver Constituents Following Partial Hepatectomy in Rats. *Mary E. Dumm,* and *Elaine P. Ralli.*

77. The Place of Anorexic Agents in Weight Reduction. *E. Philip Gelvin,* and *Thomas H. McGavack.*

78. Acromegaly—Case Presentations, Hormonal and Radiation Therapy. *Rita S. Finkler,* and *George M. Cohn.*

79. Influence of Thyrotrophic Hormone (TSH) and Thiouracil on the Oxygen Consumption of the Guinea Pig. *Elizabeth A. Herrold* (by invitation), *Roy K. Rinehart* (by invitation), *Harold S. Coombs* (by invitation), and *James H. Leathem.*

80. The Use of Thyrotropic Hormone (TSH) in the Diagnosis of Myxedema. *Lester M. Levy* (by invitation), *Agamemnon Despopoulos* (by invitation), and *William H. Perloff.*

81. Blood Radioiodine Concentration and Blood Radiation Dosage During I^{131} Therapy for Metastatic Thyroid Carcinoma. *S. M. Seidlin, A. Aaron Yalow* (by invitation), and *Edward Siegal,* (by invitation).

82. Incapacitating Masked Hyperthyroidism Successfully Treated with the Imidazoles. *Jacqueline Chevalley,* and *Thomas H. McGavack.*

83. Chronic Thyrotoxic Myopathy. *Edward L. Quinn* (by invitation) and *Richard L. Worcester* (by invitation) (introduced by J. P. Pratt).

84. Refractoriness to Anti-Tetanic Therapy. Occurrence in a Case of Surgical Hypoparathyroidism. *Major Raymond W. Blohm, Jr.,* and *Lt. Col. Otto A. Wurl* (introduced by Roberto F. Escamilla).

85. The Antagonistic Effect of Various Steroids to Testosterone and Estrogen-Induced Changes in the Castrate Rodent. *F. C. Dohan, Arden F. Corday* (by invitation), and *V. S. Palladino* (by invitation).

86. The Relative Effectiveness of Different Androgenic Preparations on the 17-Ketosteroid Excretion in Man and Gonadotrophic Inhibition and Growth Stimulating Effects on the Male Accessory Glands in the Rat. *Herbert S. Kupperman, Betty Silver* (by invitation), and *Ralph Postiglione* (by invitation).

87. Effect of Ascorbic Acid on the Connective Tissue Reaction Induced in Guinea Pigs by Estrogen. *Wm. V. B. Robertson, F. W. Dunihue,* and *E. C. Sanborn* (introduced by W. Raab).

88. The Effect of Daily Injections of Progesterone on the Persistent Estrus Produced in Rats by Hypothalmic Lesions. *Monte A. Greer.*

89. Induction of Cystic Endometrial Hyperplasia in the Hamster with Estradiol; Prevention and Treatment with Progesterone. *A. E. Rakoff, Mona L. Gross* (by invitation), and *B. L. Wellenbach* (by invitation).

90. The Role of the Pituitary and Steroid Hormones in Growth Changes of the Cervix. *H. E. Nieburgs* and *Lane H. Allen* (by invitation).

91. Some Hormone Studies During Normal and Toxemic Pregnancy. *C. W. Lloyd, E. C. Hughes* (by invitation), *J. Lobotsky* (by invitation), and *J. Rienzo* (by invitation).

92. Effects of Testosterone Propionate on Human Ovulation. *Edwin C. Jungck, Willis E. Brown,* and *Byron A. Bennett* (by invitation).

93. Dysmenorrhea—Its Effective Control by Preovulary Administration of Methyl Testosterone or Androstenediol without Inhibition of Ovulation. *Stanley J. Goodman* (by invitation), and *Herbert S. Kupperman.*

94. Effective Control of the Surgical Menopause by Estradiol Implantation at the Time of Oophorectomy and Total Hysterectomy. *Herbert S. Kupperman Robert W. Delaplaine* (by invitation), and *John R. Bottomy* (by invitation).

95. Clinical Effectiveness of a Diethylstilbestrol-Methyltestosterone Mixture in the Climacterium. *A. M. Shearman,* and *Thomas H. McGavack.*

96. An Intensive Three-Day Course of Stilbestrol in the Treatment of Anovulation. *Abner I. Weisman.*

97. The Effects of a Single Preovulatory Injection of Progesterone on Indices of Ovulation in Women. *Irving Rothchild,* and *Nan Kyung Koh* (by invitation).

98. The Therapeutic Use of Pregnandiol. *George P. Heckel.*

99. Improved Spermatogenesis After Intensive Liver Regimen With and Without Testosterone in the Therapy of Oligospermia. *S. J. Glass,* and *Murray Russell* (by invitation).

100. Male Pseudohermaphroditism, A Familial Occurrence. *Robert W. Schneider,* and *Ray Van Ommen.*

101. Relationship of Ascorbic Acid to Adrenocortical Function in Guinea Pigs. *Albert B. Eisenstein,* and *Robert E. Shank* (introduced by Cyril M. MacBryde).

102. Increased Excretion of Formaldehydogenic ("FG") Substances in the Urine of Scorbutic Guinea Pigs. *Eli M. Nadel,* and *John J. Schneider* (introduced by Abraham Cantarow).

103. The Effect of Alcohol on the Adrenal Ascorbic Acid and Cholesterol of the Rat. *James J. Smith.*

104. Maternal and Fetal Adrenal Cortical Interrelationships. *J. M. Jones* (by invitation), *C. W. Lloyd,* and *T. C. Wyatt* (by invitation).

105. Some Factors Involved in the Assay of Adrenal Cortical Hormones by the Mouse Eosinopenic Procedure. *Robert S. Speirs* (introduced by R. K. Meyer).

106. Adrenal Cortical Function at Death as Measured by the Level of Circulating Eosinophils. *Paul B. Jennings* (introduced by Matthew Molitch).

107. Inability of ACTH and Cortisone to Alter A Physiological Human Hypersensitivity Regularly Abolished by Pregnancy. *William Q. Wolfson, William D. Robinson* (by invitation), and *Ivan F. Duff* (by invitation).

108. Metabolic and Cardiovascular Effects of Various Steroids Alone and in Combination. *G. M. C. Masson* (by invitation), *A. C. Corcoran,* and *Irvine H. Page.*

109. The Effects of Adrenocortical Hormones on the Distribution and Kinetics of Body Water. *I. S. Edelman* (by invitation), and *D. L. Wilson* (by invitation), (introduced by G. W. Thorn).

110. Further Studies on Hormonal Control of Serum Lipid Partition. *David Adlersberg, Stanley R. Drachman* (by invitation), and *Louis E. Schaefer* (by invitation).

111. Clinical Observations on the Effects of Cortisone and ACTH on the Peripheral Vascular Bed. *M. James Whitelaw.*

112. Observations on the Use of Oral Cortisone and ACTH in the Open Treatment of Burns. *M. James Whitelaw.*

113. The Effects of ACTH on Scorpion Neurotoxin. *M. James Whitelaw,* and *Herbert Stahnke* (by invitation).

114. The Relationship Between B.M.R. and 17-KS. Output in Rheumatic Patients Under the Influence of Cortisone. *Manuel M. Villaverde* and *Luis Perez Montes* (by invitation).

115. The Inhibition of Adrenal Function by Cortisone, in Rheumatic Patients. *Manuel M. Villaverde.*

116. A Patient with Cushing's Syndrome: Metabolic Effects of Potassium Acetate, Adrenocorticotropin, Cortisone, Methyltestosterone and Desoxycorticosterone. *Grant W. Liddle* (by invitation), *Leslie L. Bennett,* and *Joseph E. Giansiracusa* (by invitation).

117. Evidence for "Salt-Losing" Adrenal Hormone in Congenital Adrenal Virilism Associated with Addisonian-Like Symptoms. *Joseph W. Jailer.*

118. Estrogen-Producing Tumors of the Adrenal. Report of Four Cases. *Edward Rose, F. C. Dohan, Harold F. Zintel* (by invitation), and *John W. Eiman* (by invitation).

119. The Use of ACTH and Cortisone in the Management of Acute Abdominal Emergencies. *Lenore Boling* (by invitation), *John Newkirk* (by invitation), *Phillip Baxter* (by invitation), *Sheldon Margen,* and *Laurance W. Kinsell.*

210. Effect of Oral and Intrasplenic Administration of Cortisone. *A. M. de Andino,* and *J. L. Rivero-Fontan* (introduced by Karl E. Paschkis).

121. An Excellently Tolerated, Heat-Stable, Long-Acting ACTH Preparation Suitable for Prolonged and Ambulatory Treatment. *William Q. Wolfson, Robert E. Thompson* (by invitation), *William D. Robinson* (by invitation), *Leon Lewis* (by invitation), and *Ivan F. Duff* (by invitation).

122. Effect of Alanine Pyruvate and Glutamate on Insulin Reaction in Mice. *George R. Fisher* (introduced by Karl E. Paschkis).

123. Diabetogenic Effect of Insulin on Glucose Tolerance Tests in Normal Individuals. *B. A. Watson,* and *D. W. Jones* (by invitation).

124. Pre-Adolescent Hyperantuitarism in Diabetes Mellitus. *Carlos P. Lamar.*

Fourth Annual Postgraduate Assembly in Endocrinology Including Diabetes

Sponsored by

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

and

THE AMERICAN DIABETES ASSOCIATION

SEATTLE, WASHINGTON OLYMPIC HOTEL JULY 2–7, 1951

The faculty will consist of prominent researchers and clinicians in the field of endocrinology and metabolic disorders.

The course will be a practical one of interest and value to the specialist and those in general practice. The program will consist of lectures, clinics, and demonstrations. Ample time will be given to questions and answers at the end of each session, and registrants are encouraged to contact members of the faculty for individual discussions.

The Olympic, one of Seattle's most delightful hotels, offers special convention rates to members of this assembly. This is an unusual opportunity for you and your family to enjoy a pleasant vacation in the beautiful Pacific Northwest and for you to participate in a highly instructive program of the latest advances in endocrinology and metabolism.

A fee of $75 will be charged for the entire course and the attendance will be limited to 100. REGISTRATION WILL BE IN THE ORDER OF CHECKS RECEIVED AND WILL CLOSE ON JUNE 4, 1951. SHOULD THERE BE AN INSUFFICIENT NUMBER OF APPLICANTS TO FILL THE COURSE, THE REGISTRATION FEE WILL BE REFUNDED IMMEDIATELY IN ITS FULL AMOUNT.

Please forward application on your letterhead, together with check payable to The Association for the Study of Internal Secretions, to Henry H. Turner, M.D., Secretary-Treasurer, 1200 North Walker Street, Oklahoma City 3, Oklahoma, *before June 4, 1951*. Further information and program will be furnished upon request.

Hotel reservations should be made directly with the Olympic Hotel, Seattle, Washington, and the hotel advised that you are attending this Postgraduate Assembly.

The American Goiter Association

THE 1951 ANNUAL MEETING

THE 1951 annual meeting of the American Goiter Association will be held in Columbus, Ohio, on May 24, 25, and 26. The Deshler-Wallick Hotel, Broad and High Streets, will be the headquarters and every effort will be made by the hotel officials to make the meeting a success and the visit a very pleasant one. It would be well to see that reservations are made now.

The president, Dr. T. C. Davison, and the chairman of the Local Arrangements Committee, Dr. George Curtis, are planning an excellent meeting which will consist of papers dealing with goiter and other diseases of the thyroid gland, dry clinics and demonstrations. It is hoped that there will be a large attendance of members.

GEORGE C. SHIVERS, M.D.,
Corresponding Secretary,
Colorado Springs, Colo.

(For the program, *see* the April issue of the Journal.)

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE (1952)

Organized by the British Board of Management of the International Federation of Physical Medicine

Preliminary Notice

President:	Lord Horder
Vice-Presidents:	Dr. Frank Howitt (Treasurer)
	Dr. Philippe Bauwens (Chairman of the Executive Committee)
	Dr. Frank S. Cooksey
Hon. Secretary:	Dr. A. C. Boyle

Address: 45, Lincoln's Inn Fields, London, W.C.2.

The Congress will be held in London, *July 14–19, 1952.*

In accordance with the regulations of the International Federation of Physical Medicine, the meetings of the Congress will be reserved for matters dealing with the clinical, remedial, prophylactic and educational aspects of Physical Medicine and with the diagnostic and therapeutic methods employed in Physical Medicine and Rehabilitation.

Technical, scientific and historical exhibitions also will be arranged.

In addition to the Scientific Programme, a full programme of social events and entertainment is being planned for the members and associate members. Arrangements for London and provincial visits of scientific and historical interest are also being made for the Congress week and the following week.

This is a preliminary notice and full details will be published later. *Applications for the Provisional Programme* should be addressed to the Honorary Secretary, International Congress of Physical Medicine (*1952*) 45, Lincoln's Inn Fields, London, W.C.2.

ENDOCRINOLOGY INDEX

The Association for the Study of Internal Secretions has undertaken to prepare a comprehensive Index of the articles published in *Endocrinology.* This Index will appear in three volumes. Volume III, covering papers published in 1940 through June, 1947, in volumes 26–40 of the journal, has been completed and is now available for distribution. Volumes I and II of the Index have not yet been completed.

Volume III of the Index is available gratis to members of the Association for the Study of Internal Secretions. The price to all non-members is $2.50. Inquiries and orders should be addressed to:

Dr. H. H. Turner, Secretary
1200 North Walker Street
Oklahoma City 3, Oklahoma.